Model of Chemotherapy-Induced Myelosuppression With Parameter Consistency Across Drugs

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Purpose: **To develop a semimechanistic pharmacokinetic-pharmacodynamic model describing chemotherapy-induced myelosuppression through drug-specific parameters and system-related parameters, which are common to all drugs.**

Patients and Methods: **Patient leukocyte and neutrophil data after administration of docetaxel, paclitaxel, and etoposide were used to develop the model, which was also applied to myelosuppression data from 2′-deoxy-2′-methylidenecytidine (DMDC), irinotecan (CPT-11), and vinflunine administrations. The model consisted of a proliferating compartment that was sensitive to drugs, three transit compartments that represented maturation, and a compartment of circulating blood cells. Three system-related parameters were estimated: baseline, mean transit time, and a feedback parameter. Drug concentration-time profiles affected the proliferation of sensitive cells by either an inhibitory linear model or an inhibitory E_{max} model. To evaluate the model, system-related parameters were fixed to the same values for all drugs, which were based on the results from the estimations, and only drug-specific parameters were estimated. All modeling was performed using NONMEM software.**

Results: **For all investigated drugs, the model successfully described myelosuppression. Consecutive courses and different schedules of administration were also well characterized. Similar system-related parameter estimates were obtained for the different drugs and also for leukocytes compared with neutrophils. In addition, when system-related parameters were fixed, the model well characterized chemotherapy-induced myelosuppression for the different drugs.**

Conclusion: **This model predicted myelosuppression after administration of one of several different chemotherapeutic drugs. In addition, with fixed system-related parameters to proposed values, and only drug-related parameters estimated, myelosuppression can be predicted. We propose that this model can be a useful tool in the development of anticancer drugs and therapies.**

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OPTIMIZATION OF DOSES and administration schedules for anticancer agents is desirable not only in the development of new drugs but also for established drugs. One component in optimizing cancer therapies is to establish relationships between drug concentrations and myelosuppression, which is dose limiting for most anticancer drugs. Typically, a summary variable of drug exposure (eg, area under the concentration *v* time-curve) is related to the observed nadir value. Therapeutically relevant information regarding the time course of exposure and duration of neutropenia, which is directly related to the risk of infection,[1] is wasted in such cases. Consequently, models that can explain and predict both the degree and duration of hematological toxicity, after different schedules of administration, are of a particular value.

Empirical models of the relationship between the exposure and the whole time course of leukopenia have been developed.[2,3] However, more physiology-based models are preferred because they generally are more predictive, with parameters that refer to actual processes and conditions. Ideal physiology-based models separate system parameters, common across drugs, from drug-specific parameters. It is therefore desirable that differences between drugs should be reflected solely by drug-related parameters, because parameters inherent to the biologic system are not dependent on the drug administered. The application of such a model under various clinical settings is possible, as the model can account for changes in physiological functioning. Patient characteristics can be incorporated, and these characteristics can help in identifying therapeutic subgroups and improve patient predictions. Separation of system- and drug-related parameters is common in physiology-based pharmacokinetic modeling, whereas system-related parameters are generally fixed to literature values. This concept has also been applied in pharmacokinetic-pharmacodynamic modeling (eg, by van der Graaf et al[4]), but there, system-related parameters are generally estimated.

A few physiologically based pharmacokinetic-pharmacodynamic models have been established to estimate the entire time course of myelosuppression.[5-8] The architecture and kinetics of granulocytopoiesis form the physiological basis of these models. In the indirect model,[5] a lag time accounted for the delay in leukocyte decrease. In the other models,[6-8] transit compartments[9] predicted the time delay that mimics the maturation chain in the bone marrow. One model[7] also included a feedback parameter that explained the overshoot of leukocytes, which is necessary to adequately model successive courses.

Our previous models[6,7] used relatively rich pharmacodynamic data, especially in the model of rat leukocytes,[7] where measurements were made every other day, after three different administration schedules. However, samples usually are taken more sparsely in the clinic, and data sets are often incomplete. Sparse pharmacodynamic data impose limitations on the complexity of the model. Therefore, we wanted to develop a less complex

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model with interpretable system-related parameters, and the model should be applicable across drugs.

PATIENTS AND METHODS

Patients, Treatments, and Measurements

Only patients who received a single anticancer agent were included in the data analyses. Patients known to have received granulocyte colony-stimulating factor (G-CSF) therapy were excluded. For those time points when neutrophil counts were missing, leukocyte data were also omitted so that leukocyte and neutrophil analyses could be compared. Observed neutrophils during the first course are shown in Fig 1. Total concentrations were used in the modeling, except for paclitaxel, where unbound concentrations were used. All patients signed informed consent forms, and local human investigation committees at each participating institution approved the studies.

Docetaxel. Leukocytes and neutrophils (3,553 observations of each type) from 601 patients in 24 phase II studies[10] at first cycle of treatment were used. Median baseline values were 7.0 and 4.9 $\times$ 10^9/L for leukocytes and neutrophils, respectively. Patients received a dose of 75 or 100 mg/m^2, most of them as a 1-hour infusion, but for a few patients, two or three short infusions were given. Individual-specific parameters from an earlier presented pharmacokinetic population model[11] were used to generate concentration-time profiles.

Paclitaxel. Leukocytes and neutrophils (530 observations of each type) from 45 patients with different cancer forms, who received paclitaxel in a total of 196 cycles (varying between one and 18 cycles per patient; median, three cycles), were analyzed. In addition to these 45 patients, the study included three additional patients with high and increasing values of leukocytes who were excluded in the modeling to get a successful minimization. Median baseline values were 7.6 and 5.5 $\times$ 10^9/L for leukocytes and neutrophils, respectively. Paclitaxel was administered as a 3-hour infusion, with an initial dose of 175 mg/m^2 every 3rd week. Dose adjustments were guided by hematological and nonhematological toxicity, which resulted in a final dose range of 110 to 232 mg/m^2. Plasma concentrations were monitored on course 1 and course 3, with an average of 3.5 samples per patient and course. Individual unbound concentration-time profiles were obtained by using doses and empirical Bayes estimates (based on measured concentrations of unbound paclitaxel) from a mechanism-based population pharmacokinetic model.[12] Population-typical values were used in five individuals who lacked pharmacokinetic observations.

Etoposide. Leukocytes and neutrophils (682 observations of each type) from two studies,[13,14] with a total of 71 patients who received a 3-day

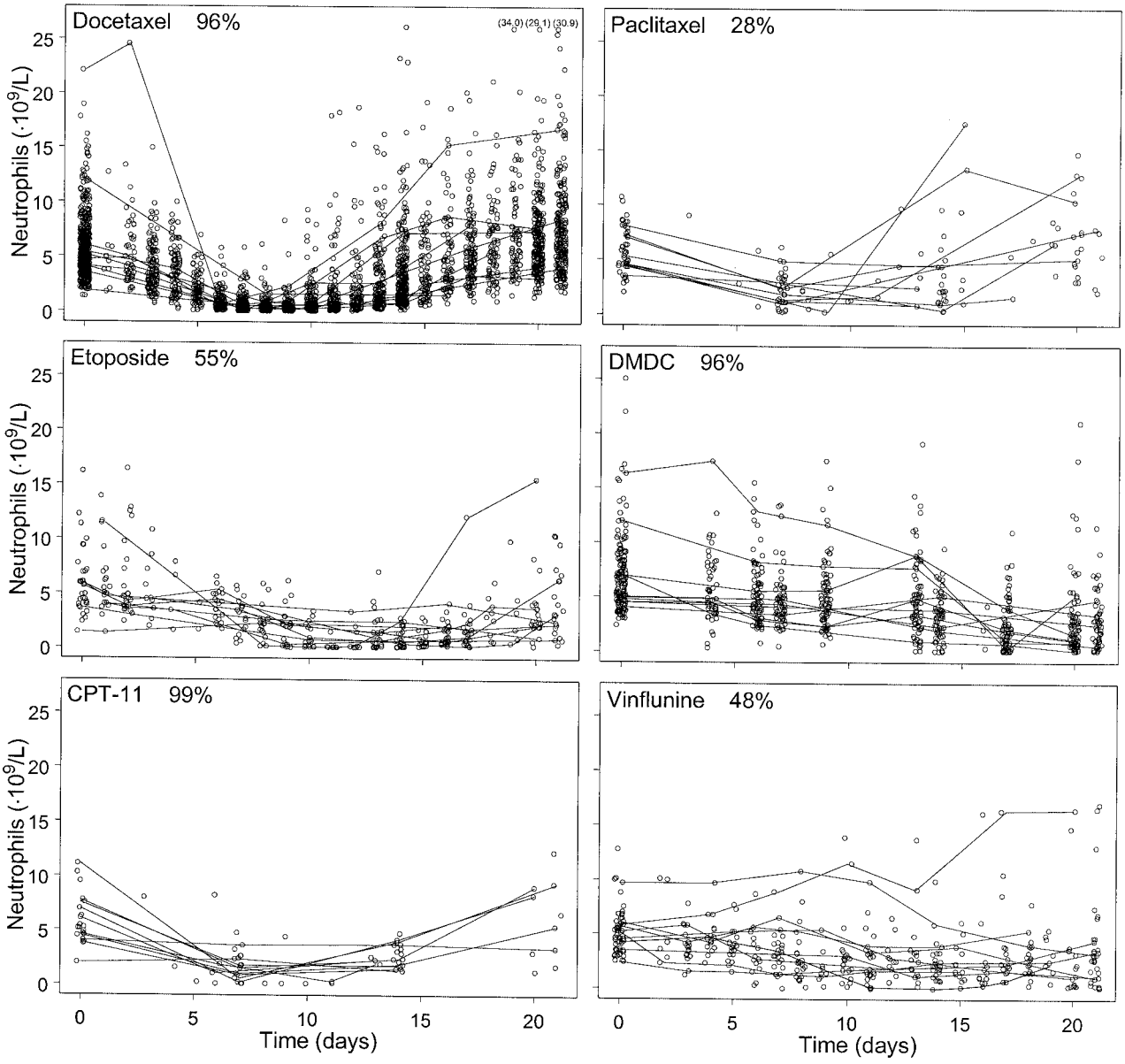

Fig 1. Neutrophil observations during the first 3 weeks, after the first dose. For 10 randomly selected patients, the individual observations have been connected with lines. Shown are also the percentages of data points used in the analyses that are within the time frame of the x-axes.

continuous infusion, were used. Median baseline values were 7.3 and 4.9 $\times$ 10^9/L for leukocytes and neutrophils, respectively. The standard total dose was 375 mg/m^2, but in the individualized groups, the total delivered dose ranged from 225 to 789 mg/m^2. A second course of treatment was administered to 47 of the patients at least 4 weeks after first treatment. However, we lacked information on exactly when the second course started, so we assumed that the leukocyte and neutrophil counts had returned to baseline before the start of the second course (ie, no carryover effect from the previous dose was considered). Concentration-time profiles were calculated, based on actual steady-state concentrations and a literature value of the elimination half-life (7.5 hours, within the common range of values previously reported),[15] according to

$$C = C_{ave} \cdot (1 - e^{-kt}) \text{ from 0 to 72 hours} \quad (1)$$

$$C = C_{ave} \cdot e^{-kt_{inf}} \text{ from } > 72 \text{ hours} \quad (2)$$

where C = concentration, C_{ave} = average steady state concentration, k = elimination rate constant ($ln2/t_{1/2}$), t = time from the start of the infusion, and t_{inf} = time from the end of the infusion.

2′-deoxy-2′- methylidenecytidine (DMDC). The data set included 65 patients who received an oral once-daily regimen for 7, 10, or 14 days and 85 patients who received an oral bid regimen for 7 or 10 days. Total daily doses ranged from 12 to 50 mg/m^2, and the patients were observed during the first course (ie, for 21 to 28 days).[16-18] In two patients, neutrophil values increased from $< 0.25 \times 10^9$/L to $> 30 \times 10^9$/L in 3 days. Reasons for the steep rebound could be infection or G-CSF administration (information not available). To get successful minimization, these high values were excluded. A total of 823 observations each, for leukocytes and neutrophils, was modeled. Median baseline values were 8.9 and 6.2 $\times$ 10^9/L for leukocytes and neutrophils, respectively. Individual concentration-time profiles were obtained using doses and empirical Bayes estimates.[19]

Irinotecan (CPT-11). Leukocytes and neutrophils from 20 patients (79 observations of each type), during the first 21 days after receiving 350 mg/m^2 CPT-11 as a 1.5-hour infusion, were included.[20] Median baseline values were 7.8 and 5.2 $\times$ 10^9/L for leukocytes and neutrophils, respectively. Total drug concentrations (lactone and carboxyl acid forms) of CPT-11 and the active metabolite, SN-38, were inserted into the data set. Concentration-time profiles were obtained by interpolation between observed concentrations and log-linear extrapolation from the last observed concentration.

Vinflunine. Fifty-nine patients, on a total of 191 courses (842 observations each of leukocytes and neutrophils) from three phase I studies, were included.[21-23] Median baseline values were 7.0 and 4.8 $\times$ 10^9/L for leukocytes and neutrophils, respectively. Three different dose schedules were given: one administration every 3 weeks (30 to 400 mg/m^2, 30 patients); weekly administration, where one course is 4 weeks (120 to 190 mg/m^2, 14 patients); and administration on day 1 and day 8 every 3 weeks (170 to 210 mg/m^2, 15 patients). All administrations were 10-minute infusions. Individual concentration-time profiles were based on an average of 14 concentration measurements (range, 10 to 15 concentration measurements) per patient, sampled predose and in the interval of 5 minutes to 168 hours after start of the infusion. More limited concentration measurements were also made during subsequent administrations. Log-transformed leukocyte and neutrophil counts were used in the vinflunine modeling.

Model development. The docetaxel, paclitaxel, and etoposide data sets were used to develop the final structural model (Fig 2), which consisted of one compartment that represented stem cells and progenitor cells (ie, proliferative cells [*Prol*]), three transit compartments with maturing cells (*Transit*), and a compartment of circulating observed blood cells (*Circ*). A maturation chain, with transit compartments and rate constants (k_{tr}), allowed prediction of a time delay between administration and the observed effect. The generation of new cells in *Prol* was dependent on the number of cells in the compartment; that is, self-renewal or mitosis, a proliferation rate constant determining the rate of cell division (k_{prol}), and a feedback mechanism from the circulating cells $(Circ_0/Circ)^{\gamma}$. The feedback loop was necessary to describe the rebound of cells (ie, an overshoot compared with the baseline value [$Circ_0$]). It was incorporated in this way because it is known that the proliferation rate can be affected by endogenous growth factors and cytokines[24] and that circulating neutrophil counts and the growth factor G-CSF levels are inversely related.[25] The differential equations were written as

$$dProl/dt = k_{prol} \cdot Prol \cdot (1 - E_{Drug}) \cdot (Circ_0/Circ)^{\gamma} - k_{tr} \cdot Prol \quad (3)$$

$$dTransit1/dt = k_{tr} \cdot Prol - k_{tr} \cdot Transit1 \quad (4)$$

$$dTransit2/dt = k_{tr} \cdot Transit1 - k_{tr} \cdot Transit2 \quad (5)$$

$$dTransit3/dt = k_{tr} \cdot Transit2 - k_{tr} \cdot Transit3 \quad (6)$$

$$dCirc/dt = k_{tr} \cdot Transit3 - k_{circ} \cdot Circ \quad (7)$$

The drug concentration in the central compartment (*Conc*) is assumed to reduce the proliferation rate or induce cell loss by the function E_{Drug}, which was modeled to be either a linear function (*Slope* $\times$ *Conc*) or an E_{max} model, $E_{max} \times Conc/(EC_{50} + Conc)$. In the transit compartments, it is assumed that the only loss of cells is into the next compartment. As the proliferative cells differentiate into more mature cell types, the concentration of cells is maintained by cell division. At steady state, $dProl/d\,t = 0$, and therefore $k_{prol} = k_{tr}$. To minimize the number of parameters to be estimated, it was assumed in the modeling that $k_{circ} = k_{tr}$. To improve interpretability, the mean transit time was estimated, which was defined as $MTT = (n + 1)/k_{tr}$, where n is the number of transit compartments. Thus, the structural model parameters to be estimated were $Circ_0$, *MTT*, γ, and *Slope* (or E_{max} and EC_{50}). For consistency, interindividual variability was always (and only) estimated on $Circ_0$, *MTT*, and *Slope* (or EC_{50}). To calculate $Slope_u$, that is, *Slope* based on unbound concentrations (or *Slope* for paclitaxel), unbound fractions of 0.02 (docetaxel),[26] 0.05 (paclitaxel),[27] 0.14 (etoposide),[28] 0.97 (DMDC),[19] 0.37 (CPT-11),[29] and 0.22 (vinflunine, Pierre-Fabre, Castres, France; data on file) were used.

Data analysis. All different drugs were fitted separately. The model parameters were estimated in a nonlinear mixed effects ("population") analysis, where data from all patients were analyzed simultaneously. The population model parameters estimated were fixed effects, related to the typical individual, and random effects, with magnitudes of interindividual variability (IIV) in parameters and magnitude of residual variability between individual predictions and observations. Log-normal parameter distributions were used for the IIV as follows:

$$P_i = TVP \cdot exp(\eta_i) \quad (8)$$

where *TVP* is the population typical value, P_i is the individual parameter value, and η_i represents the individual deviation. The ηs are symmetrically distributed zero-mean random variables, with a variance estimated as part of

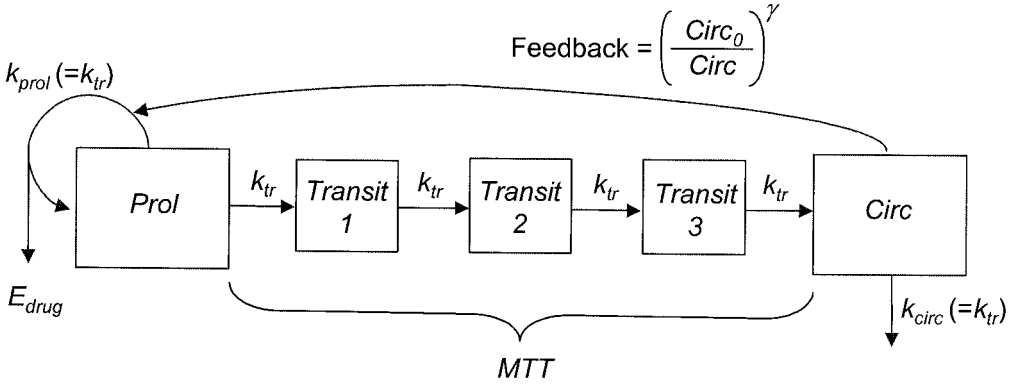

Fig 2. The structure of the pharmacokinetic-pharmacodynamic model describing chemotherapy-induced myelosuppression for all investigated drugs.

the model. The residual error was modeled with an additive and a proportional component, either of which was excluded if not necessary to adequately describe the data. The analyses were performed using NONMEM (Version VI beta).[30] The first-order methods implemented in NONMEM are based on first-order Taylor series linearizations of the prediction, with respect to the dependence on parameters. The derivative of the function can be evaluated at the value of the population (FO method) or individual (FOCE method) estimate of the parameter. When the population parameter estimate is used for the derivative with respect to some parameters and the individual estimate is used for other derivatives, the method is called HYBRID. When the residual error is heteroscedastic, the residual error magnitude can be modeled as dependent on the population (no INTERACTION) or individual (INTERACTION) prediction. The former is the only possible option for the FO method, whereas for FOCE, there is a choice of using INTERACTION or not. The theoretically most attractive method is FOCE with INTERACTION, which also has shown the best properties in simulation studies,[31-33] and this method was also the method used for most analyses. However, this is the most computationally complex and computer-intensive method, and therefore, the other methods were used in some instances. Graphical diagnostics, using the S-plus (Version 2000; Insightful, Seattle, WA)-based program Xpose,[34] and comparison of competing models, using the objective function values (OFV) in the likelihood ratio test, guided the model development. A difference in OFV of > 10.83, corresponding to a significance level $P < .001$, was used for discrimination between two nested models that differed in one parameter. All predictions (population and individual) were based on individual concentration-time profiles.

RESULTS

The structural model (Fig 2) explained all data sets well (Figs 3 and 4). Toxicity profiles were also well characterized when several treatment cycles were modeled continuously in time (Figs 5 and 6), and they were valid for different schedules of administration (Fig 6). To be able to compare results, and for the sake of simplicity, the number of transit compartments was fixed to three for all drugs. Increasing or reducing the number of transit compartments (data not shown) led to little improvement in OFV. In addition, adding an effect compartment to account for the distribution of drug to the bone marrow did not improve the models. Estimated half-lives of circulating cells ($ln2/k_{tr}$) were 15 to 24 hours. There was no improvement of the fits when half-life was estimated as a separate parameter (range, 8 to 32 hours) or when fixed to a literature value of 6.7 hours.[35]

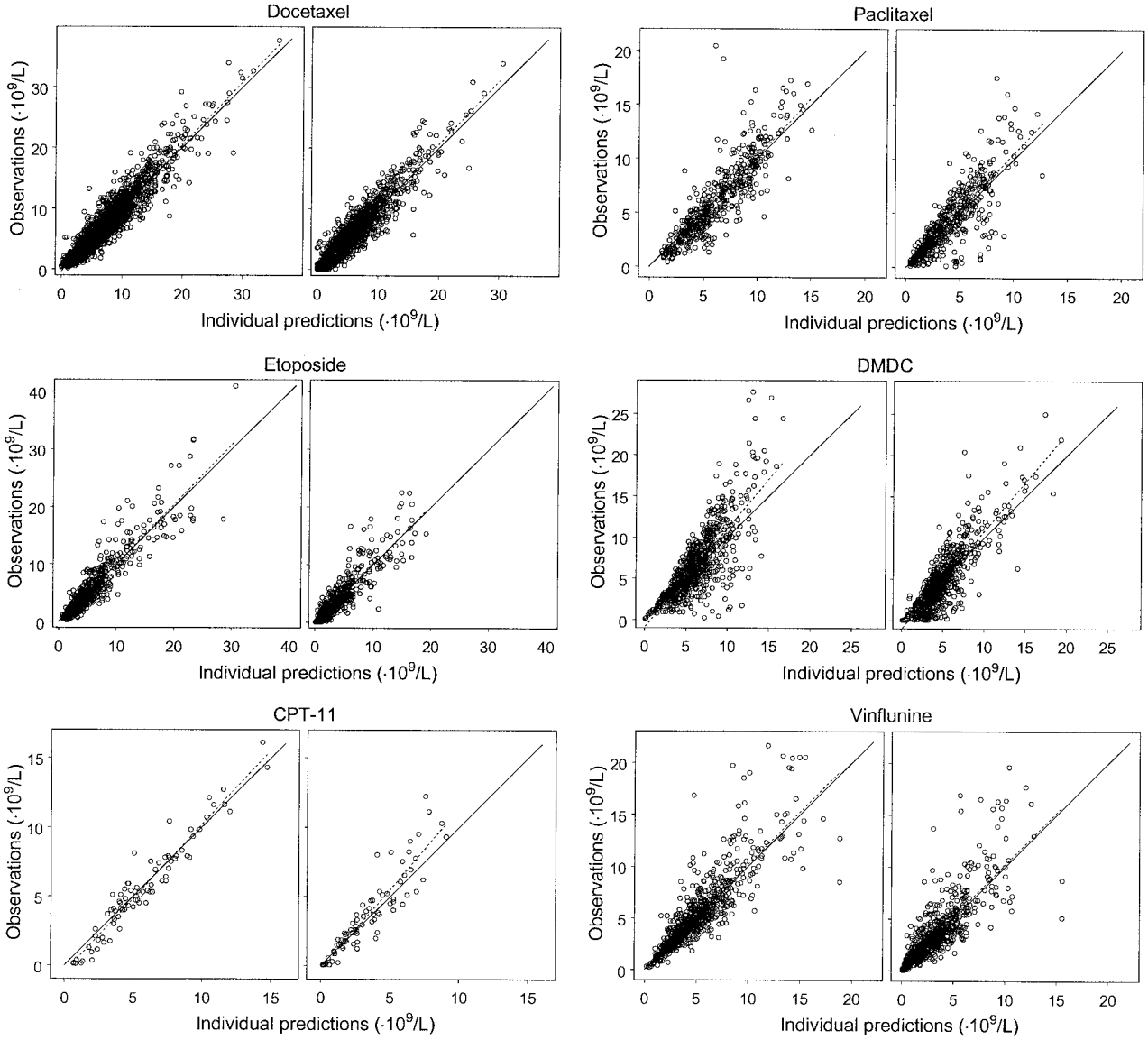

Fig 3. Observations versus individual predictions (based on empirical Bayes estimates) for leukocytes (left) and neutrophils (right). Included are lines of identity (—) and regression lines (---).

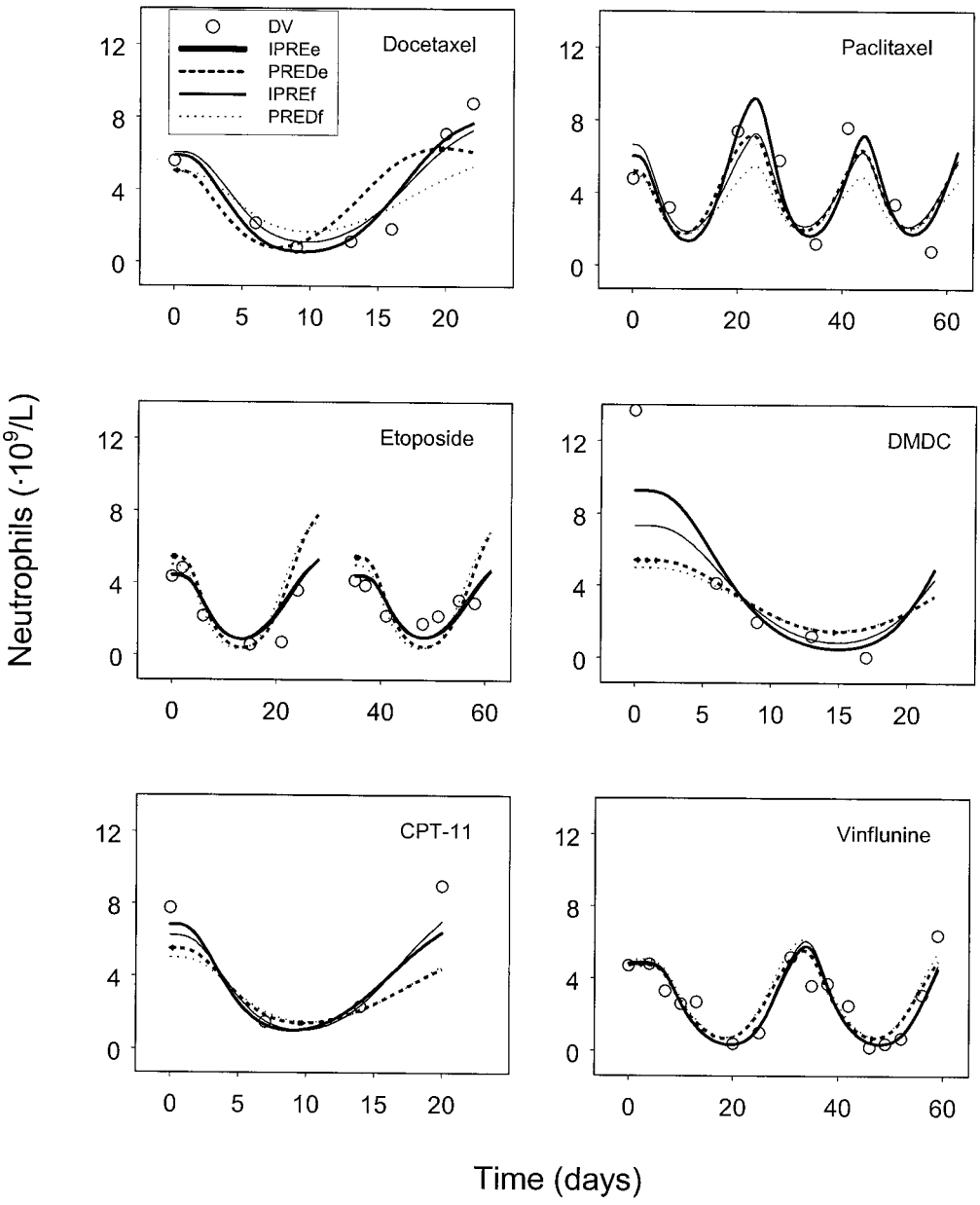

Fig 4. Observations (DV), predictions based on typical population estimates (PRED), and individual predictions (IPRE) with estimated (e) and fixed (f) system-related parameters for individuals selected on the basis of their typical residual error magnitude (the individual's average absolute weighted residual is at the population median).

In general, all drugs produced similar estimates of $Circ_0$, *MTT*, and γ, and their corresponding IIV (Tables 1 and 2). The DMDC neutrophil model was unstable, and estimates of *MTT* were dependent on which estimation method and residual error model was used. Therefore, *MTT* was fixed to the estimate in the leukocyte analysis (123 hours). The individual parameter estimates were for all data sets, except for docetaxel, centered around the population parameter estimates. For docetaxel, the median of the individual *MTT* values was 7% (leukocytes) and 8% (neutrophils) higher than the population estimate.

In most cases, leukocyte and neutrophil data produced similar parameter estimates, except that for neutrophils, $Circ_0$ was lower and the *Slope* estimate was higher (Tables 1 and 2). For CPT-11, the OFV was lower when the effect on proliferating cells was assumed to be from the parent drug, CPT-11, rather than from the metabolite, SN-38. For docetaxel, etoposide, and DMDC, E_{max} models were significantly better than a linear slope (Tables 3 and 4). However, there were only minor changes in the system-related parameter estimates, and E_{max} and EC_{50} were generally estimated with high relative standard errors.

In general, the FO method, when applied, produced a higher $Circ_0$, a shorter *MTT*, and a lower γ than did the FOCE/HYBRID methods (data not shown).

To evaluate the model and assess the generality in describing myelosuppression, system-related parameters were fixed: $Circ_0$ to 7×10^9/L (5×10^9/L for neutrophils), *MTT* to 125 hours, and γ to 0.17. IIV on $Circ_0$, *MTT*, and *Slope* were fixed to 35%, 20%, and 45%, respectively. These chosen parameter values were based on the results from the estimations (Tables 1 and 2). Similar *Slope* estimates (Fig 7), residual errors (not shown), and goodness of fit (Fig 4) were derived as when all parameters were estimated.

DISCUSSION

The derived model adequately described the observed leukocyte and neutrophil counts after administration of all investigated

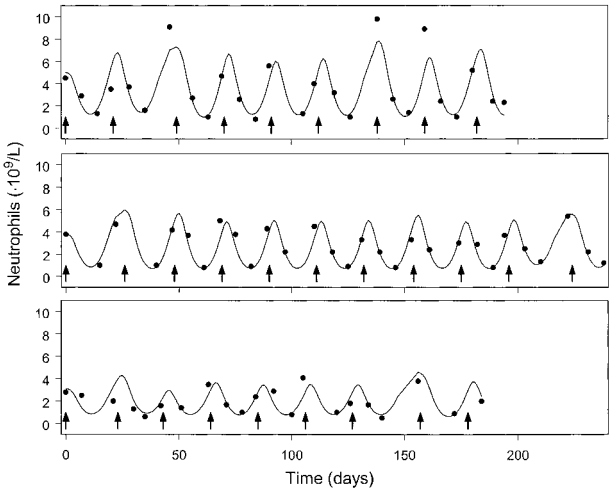

Fig 5. Individual predicted profiles (—) and observations (●) for the time-course of neutrophils in 3 patients after at least 9 successive courses of paclitaxel treatment. Arrows denote times of administration.

chemotherapeutic drugs. In agreement with the aim of mechanistically based models, many features of the present model mimic physiological theories on the structure and regulation of the granulopoietic system. System-related parameters were similar for the investigated drugs, and they were estimated with high certainty.

Estimates of the system-related parameters were nevertheless not completely void of drug influence. Part of these between-drug differences could be because, in some data sets, many patients were observed only during the first course of treatment. Therefore, less information was available on *MTT* and γ. Compared with the literature value of postmitotic transit times in healthy volunteers (6.6 days,[36] 158 hours), the estimated *MTT*s were somewhat shorter. However, myelosuppression induces release of growth factors that stimulates extra cell divisions in the proliferating compartments and shortens the time at which mature cells reach the circulation.[24] In the presence of infections, emergence times can also decrease.[37] In addition, different drugs can affect various granulopoietic cells differently. For example, compared with most other chemotherapeutic drugs, methotrexate and vinblastine cause a more rapid fall in blood counts, and melphalan and nitrosureas cause a delayed recovery after treatment.[38] In our model, all proliferative cells are in the same compartment and therefore different *MTT*s and γs are estimated to take this into account. Apart from the aforementioned possibilities, the low estimate of *MTT* for docetaxel could be because only the FO method on IIV on *MTT* was possible during the estimation. In cases where the FOCE method could be applied, longer *MTT*s were generated than with the FO method. Also, *MTT* was defined as the number of compartmental transits divided by the transit rate, k_{tr}. However, to decrease the number of parameters to be estimated, k_{tr} was also the degradation rate of circulating cells, k_{circ}. A neutrophil half-life of 6.7 hours,[35] and a lymphocyte half-life of 30 minutes,[39] have been reported in healthy volunteers, compared with our estimated half-life of 15 to 24 hours. There was most likely a lack of information about k_{circ} in the data, as an estimated or fixed half-life did not improve the fits. Also, in previous analyses, estimated half-lives of circulating neutrophils have been longer than expected (15[40] and 21[6] hours).

The extent and rate of recovery from toxicity are positively correlated with the parameter, γ. This parameter might therefore be indicative of hematopoietic viability. The feedback also provides a basis for extended models in which the effect of

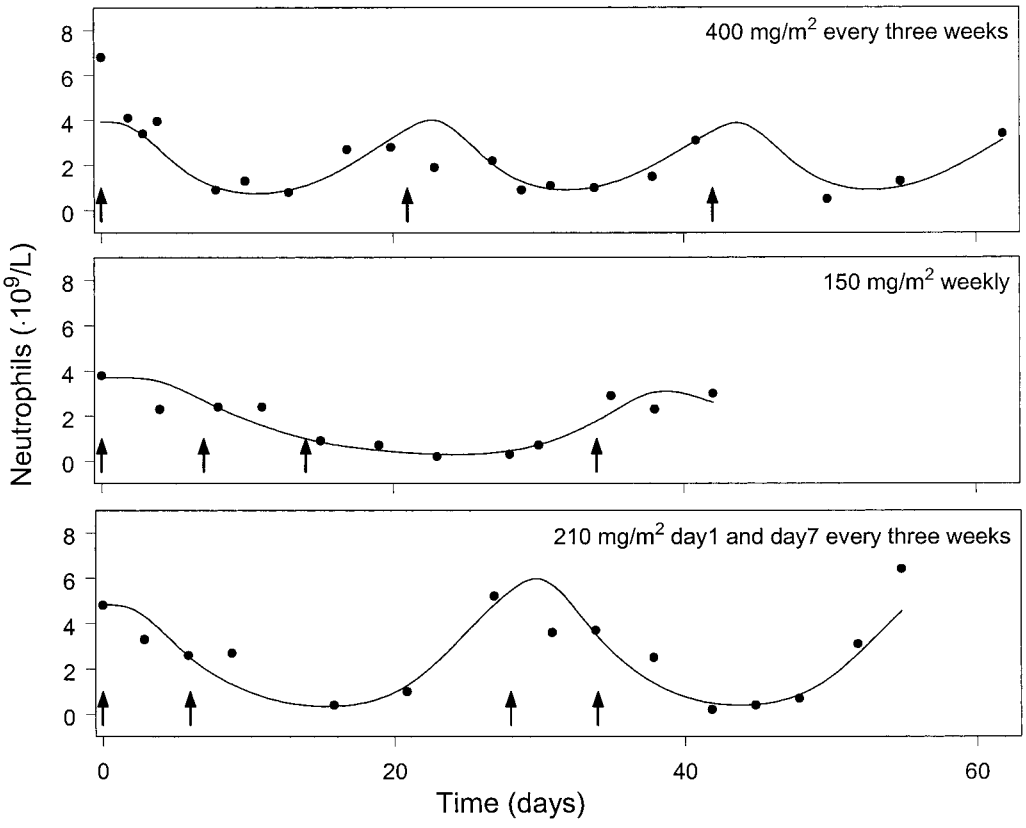

Fig 6. Individual predicted profiles (—) and observations (●) for the time course of neutrophils in 3 patients with different dose regimens of vinflunine. Arrows denote times of administration.

Table 1. Typical Population Parameter Estimates (relative SE %) for Leukocytes With a Linear Concentration-Effect Model

Drug	Estimation Method	$Circ_0$ ($\times 10^9$/L)	ω_{Circ0} (CV%)	MTT (hours)	ω_{MTT} (CV%)	γ	Slope (μM^{-1})	$Slope_u$ (μM^{-1})	ω_{Slope} (CV%)	Add ($\times 10^9$/L)	Prop (%)
Docetaxel	HYBRID (MTT, slope)	7.12 (2.1)	35 (6.8)*	90.4 (3.3)	14 (20)*	0.175 (4.7)	6.39 (6.2)	320	47 (16)*	1.31	18.9
Paclitaxel	FOCE INTER	7.21 (5.4)	33 (24)*	124 (4.7)	17 (27)*	0.239 (11)	1.45	28.9 (13)	42 (78)*	ne	28.6
Etoposide	HYBRID (MTT)	7.07 (8.2)	39 (22)*	135 (4.4)	14 (30)*	0.189 (11)	0.0710 (14)	0.508	45 (66)*	ne	41.4
DMDC	HYBRID (MTT)	7.50 (3.1)	34 (13)*	123 (16)	22 (70)*	0.121 (32)	0.660 (20)	0.680	44 (48)*	ne	37.3
CPT-11	FOCE INTER	8.10 (7.0)	26 (35)*	125 (14)	31 (53)*	0.147 (17)	0.892 (18)	2.41	40 (93)*	1.31	ne
Vinflunine	FOCE INTER	6.74 (5.5)	35 (24)*	112 (5.1)	24 (32)*	0.157 (9.0)	0.00204 (9.2)	0.00927	40 (32)*	ne	29.0

Abbreviations: ω, interindividual variability; Add, additive residual error; Prop, proportional residual error; HYBRID (MTT), the FO method was used on ω_{MTT}; ne, not estimated.

* The relative SE is related to the corresponding variance term ω^2.

Table 2. Typical Population Parameter Estimates (relative SE %) for Neutrophils With a Linear Concentration-Effect Model

Drug	Estimation Method	$Circ_0$ ($\times 10^9$/L)	ω_{Circ0} (CV%)	MTT (hours)	ω_{MTT} (CV%)	γ	Slope (μM^{-1})	$Slope_u$ (μM^{-1})	ω_{Slope} (CV%)	Add ($\times 10^9$/L)	Prop (%)
Docetaxel	HYBRID (MTT, slope)	5.05 (1.9)	42 (7.0)*	88.7 (2.5)	16 (24)*	0.161 (3.7)	8.58 (5.2)	429	60 (14)*	1.15	27.3
Paclitaxel	FOCE INTER	5.20 (3.6)	35 (11)*	127 (2.1)	18 (30)*	0.230 (2.8)	2.21	44.2 (4.5)	43 (32)*	ne	39.9
Etoposide	FOCE	5.45 (7.3)	42 (20)*	135 (3.7)	14 (23)*	0.174 (6.6)	0.126 (14)	0.899	40 (78)*	0.671	45.3
DMDC	HYBRID (MTT)	5.43 (3.9)	39 (16)*	123†	49 (23)*	0.160 (13)	0.782 (9.1)	0.806	63 (27)*	ne	48.9
CPT-11	FOCE INTER	5.51 (3.4)	29 (19)*	113 (6.9)	29 (41)*	0.132 (9.8)	1.29 (15)	3.48	43 (61)*	0.434	34.1
Vinflunine	FOCE INTER	4.72 (2.7)	41 (18)*	122 (3.7)	22 (21)*	0.162 (6.7)	0.00349 (7.8)	0.0159	41 (33)*	ne	48.0

* The relative SE is related to the corresponding variance term ω^2.

† Fixed.

Table 3. Typical Population Parameter Estimates (relative SE %) for Leukocytes With an E_{max} Model

Drug	Estimation Method	$Circ_0$ ($\times 10^9$/L)	ω_{Circ0} (CV%)	MTT (hours)	ω_{MTT} (CV%)	γ	E_{max}	Ec_{50} (μM)	$Ec_{50,u}$ (μM)	ω_{EC50} (CV%)	Add ($\times 10^9$/L)	Prop (%)
Docetaxel	HYBRID (MTT, slope)	7.10 (2.1)	35 (7.0)*	89.4 (3.3)	15 (21)*	0.175 (4.9)	50.7 (27)	5.65 (36)	0.133	61 (26)*	1.20	20.5
Etoposide	HYBRID (MTT)	7.25 (8.1)	39 (21)*	134 (3.3)	14 (24)*	0.183 (9.8)	1.09 (23)	7.64 (60)	1.07	98 (54)*	ne	40.3
DMDC	HYBRID (MTT)	7.60 (3.1)	34 (16)*	132 (11)	24 (90)*	0.133 (8.0)	0.728 (35)	0.505 (61)	0.491	94 (65)*	ne	36.0

* The relative SE is related to the corresponding variance term ω^2.

therapies with G-CSF can be studied. Typical values of baseline ($Circ_0$) were approximately the same as the medians observed, except for DMDC, which had the highest observed values, where estimated values were lower than those observed.

The same model performed well on all drugs despite the fact that drugs with differing mechanisms of action were used. Docetaxel and paclitaxel have the same mechanism of action, and the higher potency of the former drug, which is consistent with previous studies,[41] is evident from the higher $Slope_u$ value. Different $Slope_u$s could also be an indication of different drug distribution to the bone marrow. The addition of an effect compartment to account for a delay in the drug distribution, which was used in a previous study,[8] did not improve our fits. Of the IIVs estimated, the variability on *Slope* (or EC_{50}) was the highest. A large IIV in bone marrow cell toxicity of cytostatic drugs has been shown in vitro, which implies real differences in sensitivity of progenitor cells.[42]

A 100- to 1,000-fold higher cytotoxic effect of SN-38 than CPT-11 has been shown in vitro.[43] However, in our modeling, CPT-11 was the best predictor of myelosuppression, consistent with previous clinical studies.[44-46] This is not surprising, as CPT-11 in vivo has approximately 100 times higher total concentrations than SN-38, in addition to having a higher unbound fraction.[29]

The same model could be used for both leukocytes and neutrophils. *MTT* and γ were approximately the same. In these studies, 66% to 71% of the circulating leukocytes at baseline were neutrophils, which was also the case when baseline was estimated. Larger *Slope* values for neutrophils than for leukocytes show that neutrophil progenitor cells are more sensitive than lymphocyte progenitor cells.

This is the first model of myelosuppression that includes a self-renewal mechanism for the cell supply, a feedback parameter, and a clear separation of system-related and drug-related parameters, whereas the system-related parameters show consistency across drugs. The present model also contains few parameters so that small and sparse data sets can be modeled. For example, the amount of data in the CPT-11 data set was relatively low. This, together with the evaluation of the model, implies that the model could be used on even more sparse data

Table 4. Typical Population Parameter Estimates (relative SE %) for Neutrophils With an E_{max} Model

Drug	Estimation Method	$Circ_0$ ($\times 10^9$/L)	ω_{Circ0} (CV%)	MTT (hours)	ω_{MTT} (CV%)	γ	E_{max}	Ec_{50} (μM)	$Ec_{50,u}$ (μM)	ω_{EC50} (CV%)	Add ($\times 10^9$/L)	Prop (%)
Docetaxel	HYBRID (MTT, slope)	5.05 (3.0)	42 (8.0)*	89.3 (3.9)	16 (38)*	0.163 (3.9)	83.9 (33)	7.17 (50)	0.144	77 (17)*	1.14	27.2
Etoposide	FOCE	5.54 (7.4)	42 (22)*	136 (3.6)	14 (21)*	0.172 (7.3)	1.57 (17)	5.20 (54)	0.729	100 (58)*	0.663	45.0
DMDC	HYBRID (MTT)	5.46 (4.4)	40 (15)*	132†	45 (25)*	0.181 (17)	1.97 (73)	1.82 (90)	1.77	74 (38)*	ne	48.3

* The relative SE is related to the corresponding variance term ω^2.

† Fixed.

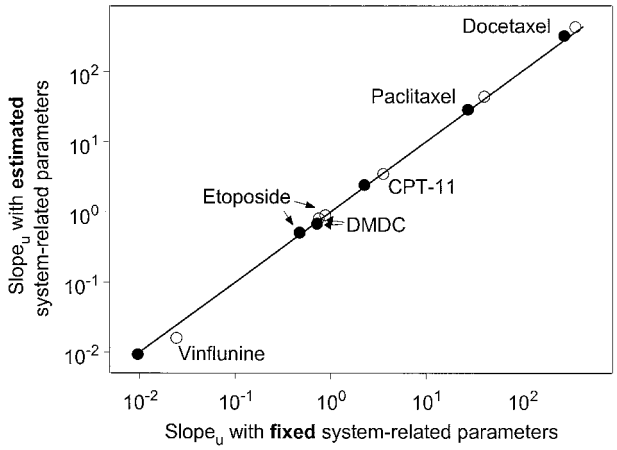

Fig 7. Slope$_u$ when system-related parameters were estimated versus Slope$_u$ when system-related parameters were fixed for leukocytes (●) and neutrophils (○).

sets that use prior information on the system-related parameters. Another advantage of this model is that the FOCE method can be used, which has been shown to produce less biased estimates than standard methods.[30,32]

In vitro and/or preclinical in vivo data could be helpful in giving a prediction of the concentration-effect relationship. By comparing relative potencies of drugs on bone marrow progenitor cells in vitro, approximate *Slope$_u$* estimates could be derived. The whole time-course of myelosuppression in patients can then be predicted for new drugs by using the suggested values of system-related parameters. The model can also be applied on preclinical in vivo data,[47] and information about *Slope*, after administration of different doses and schedules, can be used in the design of clinical studies. In addition, the model has been used to evaluate combinations of anticancer drugs in rats[47] and in patients.[48]

Further developments to the model include simultaneously analyzing data from different drugs and/or including covariate effects to explain the IIV, thereby increasing the predicting potential in clinical situations. For example, older patients with poor performance statuses exhibit increased bone marrow susceptibility to chemotherapeutic drugs,[49] and alpha$_1$-acid-glycoprotein is an independent predictor of toxicity after docetaxel administration.[10] The ability to identify risk populations is an important asset of population pharmacokinetic-pharmacodynamic modeling.

In conclusion, a simple semimechanistic model, with the consistency of system-related parameters across drugs and the ability to estimate parameters from small and sparse data sets, has been developed. This model could be a helpful tool, not only for explaining observed data but also for predictions in the design of clinical trials of new and established chemotherapy.

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