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ORIGINAL ARTICLE

Comparison of different semi-mechanistic models for chemotherapy-related neutropenia: application to BI 2536 a Plk-1 inhibitor

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Abstract
Purpose The aim of this investigation was to compare the performance of a commonly used semi-mechanistic model for drug-related neutropenia with other semi-mechanistic models published in the literature.
Methods After their implementation in NONMEM VI, five semi-mechanistic models were assessed using the pharmacokinetic and absolute neutrophil count data obtained from 95 patients with non-small cell lung cancer receiving either 200 mg on day 1 or 50 or 60 mg on days 1, 2 and 3 of a 21-day treatment course with the new Plk-1 inhibitor BI 2536. The model performance was compared by means of predictive (visual and numerical) checks, precision in the parameter estimates and objective function-based measures. Details of model parameterization, model stability and run times are also provided.
Results The time course of the drug plasma concentrations was described by a three compartment model with a first-order elimination rate. With respect to neutropenia, all models were successfully implemented in NONMEM and provided reasonable fits for the median (although not all models described all percentiles of the data well), and in general precise parameter estimates.
Conclusion In the current evaluation performed in a single drug, none of the models showed superior performance compared to the most commonly used model first described by Friberg et al. (J Clin Oncol 20:4713–4721, 2002).

Keywords BI 2536 · Semi-mechanistic models · Population model · NONMEM · Neutropenia

Introduction

Neutropenia is one of the most common adverse effects associated with cytotoxic anticancer drugs and the most serious haematologic toxicity [1, 2]. It has also been reported that absolute neutrophil counts (ANC) at nadir can be considered as a surrogate marker for dose selection to maximize efficacy, and several studies showed that a lack of haematological toxicity during cancer chemotherapy is associated with less anticancer efficacy [3, 4].

Over the last decade, a series of pharmacokinetic/pharmacodynamic (PK/PD) models have been proposed to describe these haematological effects [5–9]. Those models reflected in a simplified manner the main processes accounting for the underlying mechanisms responsible for the fate of circulating neutrophils: proliferation of progenitor cells, maturation, degradation and in some cases a feedback mechanism. The drug effects have been modelled as a function of drug concentrations in plasma (Conc) [7, 9] in an effect compartment ($Conc_e$) [6] or as a function of the area under the concentration versus time curve (AUC) [5, 8]. More complex models for granulopoiesis have also

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been described in the literature [10], which included an explicit cell-cycle structure in the mitotic compartment and detailed dynamics of the granulocyte-colony stimulating factor (G-CSF). However, due to their complexity, a greater number of equations and parameters are required that, in turn, often necessitates fixing parameters to literature values.

The semi-mechanistic PK/PD model of neutropenia first proposed by Friberg et al. [7] is currently considered the gold standard to describe the time course of ANC. The model has shown consistency in the system-related parameter across several studies involving different anticancer drugs. This model has also been used to establish animal to human predictions [11], to identify covariate effects [12], to describe or predict the toxicity of drug combination studies [13, 14] and to create a tool for neutrophil guided dose adaptation in chemotherapy [15]. However, to the best of our knowledge, the model developed by Friberg at al. [7] has not been directly compared against other published models.

If different semi-mechanistic models relying on physiological processes are available in the literature, it seems reasonable to compare and select the most appropriate one in each case. However, such comparison implies an increase in the model development efforts in terms of computing times, model implementation and model discrimination.

The main objective of the current investigation was to compare the performance of the most commonly used neutropenia model [7] with four different published PK/PD models [5, 6, 8, 9] when fitting data from a Phase II clinical trial with the cytotoxic agent BI 2536. The dihydropteridinone derivative BI 2536 is a new and highly potent inhibitor of the human Polo-like kinase 1 (Plk1). BI 2536 induces G2/M arrest and formation of abnormal mitotic figures, such as monopolar spindles. Antitumor efficacy was observed in Phase I trials with BI 2536 where the main adverse effect was reversible dose-dependent neutropenia [16]. The pharmacokinetics and the neutropenic effects of BI 2536 have been characterized previously in patients with advanced solid tumours [14, 17].

Methods

Patient population

Data from an open-label, randomized Phase II clinical trial in patients with advanced or metastatic non-small cell lung cancer (NSCLC) were used for the current analysis. All participants provided written informed consent consistent with ICH-GCP (International conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use—Good Clinical Practice) and local legislation, once the nature and the intention of the investigation were fully explained. The study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board of the ethics committee at each study site.

Data from 95 patients were available for analysis. Supplementary material (Table 1) lists the characteristics of the patient population.

Description of the study

NSCLC patients received either 200 mg BI 2536 on Day 1 (Schedule 1) or 50 or 60 mg on Days 1, 2 and 3 (Schedule 2) of a 21-day treatment course. BI 2536 was administered as 1-h intravenous infusion. Each patient was planned to receive at least two treatment courses.

Venous blood samples for the BI 2536 determination in plasma were drawn at pre-dose and 0.5, 1, 2, 4 and 120 h (Schedule 1) and at pre-dose and 1, 2, 23.92, 25, 47.92, 48.5, 49, 50, 52 and 120 (Schedule 2) h after the start of the first infusion.

Plasma concentrations of BI 2536 were determined using a fully validated high-performance liquid chromatography tandem mass spectrometry (HPLC–MS/MS) method using electrospray ionization in the positive ion mode and [D_3] BI 2536 as internal standard. Chromatography was achieved on an analytical reversed phase HPLC column with gradient elution. The calibration curves of undiluted plasma samples were linear over the range of concentrations from 0.500 to 500 ng/ml BI 2536 BS using a plasma volume of 100 or 50 µl. The method showed inaccuracy and imprecision (CV) values below 11% [17].

The absolute neutrophil count (ANC) was determined in blood at screening and on Day 1 (Days 2, and 3 only for schedule 2), 6, 11, 16 and 22 of the 21-day treatment course using standard clinical haematology methods.

Data analysis

All analyses were performed using the population approach. The first-order conditional estimation method together with the INTERACTION option was applied as implemented in NONMEM version VI [18]. The models were fit to the ANC vs time data for all cycles. None of the patients included in the current analysis had received treatment with G-CSF. The modelling was performed sequentially; initially, the PK model was developed, followed by modelling of the time course of ANC using individual model-predicted PK parameters. An exponential model was used for inter-patient variability (IPV), and residual variability was modelled using an additive error model, with data transformed into the logarithmic scale.

Description of the models

Pharmacokinetic model. The time course of the BI 2536 plasma concentrations was described by compartmental models parameterized in apparent volumes of distribution, inter-compartmental clearances and elimination clearance as previously described [14, 17].

Pharmacodynamic models. Five different models were fitted to the ANC vs time data. Figure 1 shows a schematic representation of each model. Table 1 lists the mathematical expressions of the drug effect and the synthesis of the progenitor cells, and Table 2 lists the main differences between the models.

Model 1 [7]

Model 1 was the model first described by Friberg et al. [7]. The rates of proliferation, maturation and degradation are represented by the first-order rate constants k_{syn}, k_{tr} and k_{circ}, respectively. As the assumption was made that $k_{syn} = k_{tr} = k_{circ}$, the system-related parameters were $Circ_0$, which is ANC at baseline; MTT, the mean transit (maturation) time which is equivalent to $(n+1)/k_{tr}$, where n is the number of transit compartments; and γ, the parameter governing the magnitude of the rebound. Drug effect (E_{DRUG} = Slope × Conc) has been incorporated in the model as: $k_{syn}(t) = k_{syn} \times (1 - E_{DRUG})$.

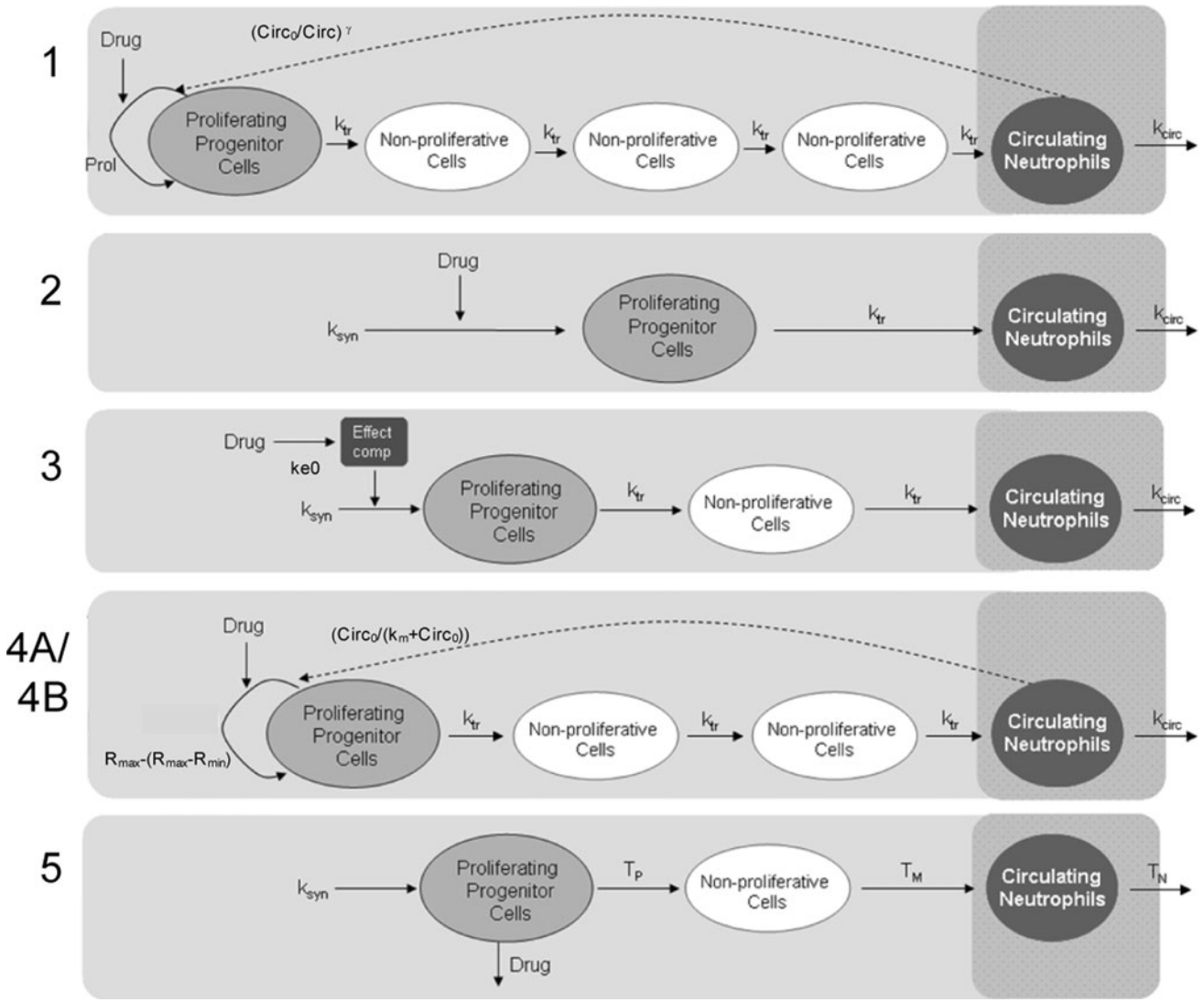

Fig. 1 Schematic representation of the different semi-mechanistic models for neutropenia. Drug, drug effect; k_{syn}, first-order (Models 1, 4A, 4B) or zero-order (Models 2, 3, 5) rate constant of proliferation; k_{tr}, 1st-order rate constant of transit; k_{circ}, 1st-order rate constant of elimination of circulating cells; γ, feedback parameter; k_{e0}, effect compartment rate constant; R_{max}, maximum proliferation rate; R_{min}, minimum proliferation rate; k_m, half saturation effect; T_P, lifespan of cells in the proliferating stage, T_M, lifespan of cells in the maturating stage and T_N, lifespan of the neutrophils

Table 1 Mathematical description of the drug effect and the proliferating progenitor cells synthesis

Model	Drug effect (E_{DRUG})	Rate of change in the progenitor compartment
1	Slope × Conc	$k_{syn} \times \left(\frac{Circ_0}{Circ}\right)^{\gamma} \times (1 - E_{DRUG}) \times PROG_{cells} - k_{tr} \times PROG_{cells}$
2	$IC/(IC + AUC_{(t)})$	$k_{syn} \times E_{DRUG} - k_{tr} \times PROG_{cells}$
	$AUC_{(t)} = \int_0^t Conc(t)dt$	
	$AUC_{(t)} = \int_{t-TS}^t Conc(t)dt \quad for \quad T \leq Ts$	
3	$IC_{50}/(IC_{50} + Conc_e)$	$k_{syn} \times E_{DRUG} - k_{tr} \times PROG_{cells}$
4A	$Conc/(IC_{50} + Conc)$	$\left(R_{max} - (R_{max} - R_{min}) \times \frac{Circ}{k_m + Circ}\right) \times (1 - E_{DRUG}) \times PROG_{cells} - k_{tr} \times PROG_{cells}$
4B	Slope × Conc	
5	$k \times Conc$	$k_{syn} - k_{syn} \times e^{-\int_{t-T_P}^{t} E_{DRUG} \times dz} - E_{DRUG} \times PROG_{cells}$

AUC drug exposure to cells during sensitive stages, *IC* AUC value that gives 50% inhibition of k_{syn}, IC_{50} drug concentration in plasma eliciting 50% inhibition of k_{syn}, *Conc*, $Conc_e$ BI 2536 plasma and effect site concencentration, respectively, k_{syn}, first-order (Models 1, 4A, 4B) or zero-order (Models 2, 3, 5) rate constant of proliferation, R_{max} maximum growth rate, R_{min} minimum growth rate, $Circ_0$ basal circulating neutrophils, k_m half saturation effect, $PROG_{cells}$ number of progenitor cells, k second-order rate constant, E_{DRUG} drug effect

Model 2 [5]

The structural model was developed by Minami et al. [5] to describe the change in leucocyte counts after a 3-h infusion of paclitaxel. The drug was assumed to inhibit the proliferation of progenitor cells, whereby cells were only sensitive to the drug for an estimated period of time (*T*s). An inhibitory E_{MAX} model was used to describe the inhibition of proliferation as a function of the area under the plasma drug concentration versus time curve (AUC) during sensitive stages of the progenitor cells. The drug-related parameter was the AUC giving a 50% inhibition of proliferation (AUC_{50}). The system parameters were the number of progenitor cells in the bone marrow ($Prog_0$), $Circ_0$, the time period in which progenitor cells are sensitive to drug (*T*s), a lag-time reflecting the onset response time (T_{LAG}), and k_{circ}. In the original analysis, k_{circ} was fixed to 0.099 h^{-1} based on the reported half-life of leucocytes [19, 20].

Model 3 [6]

Model 3 was developed by Zamboni et al. to describe neutropenia data of children and non-human primates receiving Topotecan. The original analysis was undertaken using ADAPT II software [21] to obtain individual parameter estimates. In this model, the synthesis of proliferative cells was described by a zero-order rate process which was reversibly inhibited by the predicted effect site concentrations using an inhibitory E_{MAX} model. The drug effect was represented by the drug concentration in the biophase eliciting 50% inhibition (IC_{50}). The rest of parameters estimated were k_{syn}, k_{tr}, the first-order rate constant determining concentration–time profile in the effect compartment, k_{e0}, [22] and $Circ_0$. In the original analysis, k_{circ} (=k_{syn}) was fixed to 0.099 h^{-1}.

Model 4A and model 4B [8]

In the original model described by Panetta et al. [8], data from three children with high-grade gliomas receiving temozolomide were analysed. Growth rate of proliferating cells was described by a self-renewal mechanism that was affected by a feedback term inversely proportional to the concentration of circulating neutrophils [8]. In our analysis drug inhibited the rate of proliferation as a function of plasma concentration using an inhibitory E_{MAX} model (Model 4A) or a linear model (Model 4B). The system parameters estimated were $Circ_0$, the maximum proliferation rate (R_{max}), the minimum proliferation rate (R_{min}), the half saturation effect (k_m) and the drug effect parameter either IC_{50} (Model 4A) or slope (Model 4B). At steady state, the change in the amount of cells in the proliferation compartment is zero; therefore, $k_{tr} = R_{max} - (R_{max} - R_{min}) \times Circ_0/(k_m + Circ_0)$. To reduce the number of parameters, k_{circ} was set equal to k_{tr}.

Model 5 [9]

The most recently published model to describe neutropenia is the multiple-pool cell lifespan [23, 24] proposed by Bulitta et al. A population analysis for two new formulations of paclitaxel given to adult cancer patients was performed using the software NONMEM. The progenitor (mitotic) cells were produced by a zero-order process (k_{syn}) and stayed in the proliferating pool for the lifespan T_P. Cells stayed in their maturation stage for a time equal to the lifespan T_M and finally developed to circulating neutrophils

Table 2 Main differences between the models evaluated

Model	Cell input	Time delay	Feedback effect	Drug effect	Structural parameters	Reference
1	Self-renewal	Three transit compartments	Amount of circulating neutrophils affecting rate of proliferation	Linear inhibition of proliferation of Proliferation compartment or cell loss	4	[7]
2	Zero-order rate	Lag-time	None	Inhibition of k_{syn} during sensitive stages (E_{MAX} model)	6	[5]
3	Zero-order rate	One transit compartment	None	k_{syn} inhibit by E_{MAX} model	5	[6]
4A	Self-renewal	Two transit compartments	Amount of circulating neutrophils affecting rate of proliferation	Inhibition of proliferation of Proliferation compartment by E_{MAX} model	5	[8]
4B	Self-renewal	Two transit compartments	Amount of circulating neutrophils affecting rate of proliferation	Linear inhibition of proliferation of Proliferation compartment or cell loss[a]	5	[8]
5	Zero-order rate	Lifespan model for progenitor and maturation compartment	None	Irreversible cell loss in proliferation compartment	5	[9]

[a] Drug effect in this model corresponds to the one described by Friberg et al. [7]

that stayed in blood for the lifespan T_N until degradation. The system-related model parameters estimated were $Circ_0$, T_P, T_M and T_N. Drug effect was represented by a second-order rate constant k, which elicited an irreversible loss of proliferating cells as a function of drug plasma concentration.

Comparison of the models

In contrast to the published analyses using Model 2 and 3, during the current analysis, none of the structural parameters of the models were fixed for any of the models.

Model comparison was based on the precision of the parameter estimates, and the minimum value of the objective function (MOFV) provided by NONMEM. For two nested models, a decrease of 3.84 and 6.63 in MOFV was thereby considered significant at the 5 and 1% level, respectively. In the case of comparing non-nested models, the value of the Akaike Information Criteria (AIC) [25] was used. Furthermore, prediction-corrected visual predictive checks (PC-VPC) [26] and numerical predictive checks (NPC) were performed. For PC-VPC and NPC, 500 data sets having the same design characteristics as the original data set were simulated. For the PC-VPC, both the observations and the model predictions were normalized to the typical model prediction in each bin of independent variables [27]. For the NPC, the percentage of patients developing Grade 4 neutropenia and Grade $\geq$3 neutropenia for each of the three first cycles were computed for each model. For the generation of VPC and NPC, PsN (http://psn.sourceforge.net/), Xpose version 4 (http://xpose.sourceforge.net/) and the R software (http://cran.r-project.org, version 2.6.0) were used.

Results

The 95 patients included in the analysis data set provided PK/PD data across a total of 325 cycles of therapy, with a median of 2 cycles per patient (range 1–18).

The time course of the drug plasma concentrations was described by a three compartment model with a first-order elimination rate resulting in a clearance estimate of 62.6 l/h and a total volume of distribution estimate of 3,698 l. Percentage of η-shrinkage was 13, 16 and 20% for the variability estimates in total clearance, inter-compartmental clearance between the central and deep peripheral compartments, and the apparent volume of distribution of the deep peripheral compartment, respectively. The percentage of ε-shrinkage was 4% [28]. Parameter estimates were in good agreement with previously published values [14, 17].

Models 2 and 5 had the higher number of parameters (10 parameters in total), Models 4A, B had 9 parameters in

Table 3 Parameter estimates for the neutropenia semi-mechanistic models

Parameter	Model 1	Model 2	Model 3	Model 4A	Model 4B	Model 5
AIC	−427	−20	53	−278	−363	−447
Number of parameters (typical/IPV/residual)	4/3/1	6/3/1	5/2/1	5/3/1	5/3/1	5/4/1
Computation time (relative to Model 1)	1	2.2	1	3.3	2.7	20.7
$Circ_0$ ($\times 10^9$/l)	**5.62 (4)**	**6.25 (6.77)**	**6.52 (5)**	**5.75 (5)**	**5.65 (5)**	**5.78**
$Prog_0$ ($\times 10^9$/l)	–	**5.06 (10)**	**–**	**–**	**–**	**–**
MTT (h)	**104 (2)**	–	82[b]	88[b]	103[b]	
k_{syn} (h^{-1})[e] or (Cell × h^{-1})[a]	0.0385[e]	0.214[f]	**0.195 (9)**[a]	0.0341[d]	0.0291[d]	0.0401[g]
k_{tr} (h^{-1})	0.0385[e]	–	**0.0243 (4)**	0.0341[d]	0.0291[d]	–
k_{circ} (h^{-1})	0.0385[e]	**0.0343 (15)**	0.0299[c]	0.0341[d]	0.0291[d]	–
T_{LAG} (h)	–	**80.9 (12)**	–	–	–	–
Ts (h)	–	**212 (4.18)**	–	–	–	–
γ	**0.167 (3)**	–	–	–	–	–
k_m (x 10^9/l)	–	–	–	**1.65 (41)**	**2.55 (36)**	–
R_{max} (h^{-1})	–	–	–	**0.0714 (10)**	**0.0525 (6)**	–
R_{min} (h^{-1})	–	–	–	**0.0234 (11)**	**0.0186 (16)**	–
IPV_R_{max} (%)	–	–	–	**22 (31)**	**17 (38)**	–
T_P (h)	–	–	–	–	–	**196**
T_M (h)	–	–	–	–	–	**40**
T_N (h)	–	–	–	–	–	**144**
k_{e0} (h^{-1})	–	–	**0.0169 (2)**	–	–	–
Slope (ml × ng^{-1})/IC_{50} (ng × ml^{-1})/ AUC_{50} (mg × $hxml^{-1}$)	**0.0196(6)**	**405 (18.1)**	**2.17 (12)**[2]	**13.1 (11)**[2]	**0.0277 (6)**	–
k (ml × ng^{-1} × h^{-1})	–	–	–	–	–	**0.000661**
IPV_$Circ_0$ (%)	**47 (18)**	**31 (64)**	**36 (23)**	**39 (18)**	**38 (17)**	**46**
IPV_MTT (%)	**9 (50)**	–	–	–	–	–
IPV_T_P (%)	–	–	–	–	–	**18**
IPV_T_M (%)	–	–	–	–	–	**30**
IPV_Slope/IC_{50}/IC (%)	**44 (19)**	**124 (18.4)**	**88 (19)**	**81 (24)**	**40 (22)**	–
IPV_k (%)	–	–	–	–	–	**44**
Residual error [log(Cell × 10^9/l)]	**0.44(8)**	**0.55 (6)**	**0.56 (6)**	**0.46 (8)**	**0.45 (8)**	**0.43**

Parameter estimates are listed together with the coefficient of variation [CV (%)] in parentheses. Values in bold font are estimated, and values in normal font are derived from estimated parameters. [2]Corresponds to a IC_{50} value, [a] Zero-order rate, [b] $MTT = n + 1/k_{tr}$, [c] $k_{circ} = k_{syn}/Circ_0$, [d] $k_{tr} = k_{circ} = R_{max} - (R_{max} - R_{min}) \times Circ_0/(k_m + Circ_0)$, [e] $k_{syn} = k_{tr} = k_{circ} = n + 1/MTT$, n = number of transit compartments, [f] $k_{syn} = Circ_0 \times k_{circ}$, [g] $k_{syn} = Circ_0/TN$

total, and Models 1 and 3 were the models with the lower number of parameters, 8 parameters in total. Table 3 lists the number of parameters in the models differentiating between typical and random (IPV and residual) effect parameters. The main modifications that we introduced in the model structure were the incorporation of inter-patient variability for those models that were developed under the naïve pool or two-stage approaches. Typically, we did not encounter a situation in which the addition of a random effect parameter elicited a decrease in the minimum value of the objective function greater than 40 points. The MVOF value was used as a guide to judge model performance, but it was not the main criteria. The models that are reported in the current analysis were those where the standard error of the estimates could be obtained within a NONMEM run, with the exception of Model 5. With respect to the models selected and showing the highest number of parameters, a reduction in the number of parameters always resulted in a increase in MVOF greater than 6.63 points.

Table 3 shows also the final estimates of the parameters and the corresponding precision together with the AIC values. Model 1 and 5 were the best models based on the AIC, Model 5 being slightly better than Model 1. The covariance step was successful for all models except for Model 5. The lowest residual error was obtained with Models 1 and 5 although differences between models were marginal.

The data supported estimation of IPV in $Circ_0$ and in the drug-related parameter (Slope, AUC_{50}, IC_{50} or k) for all

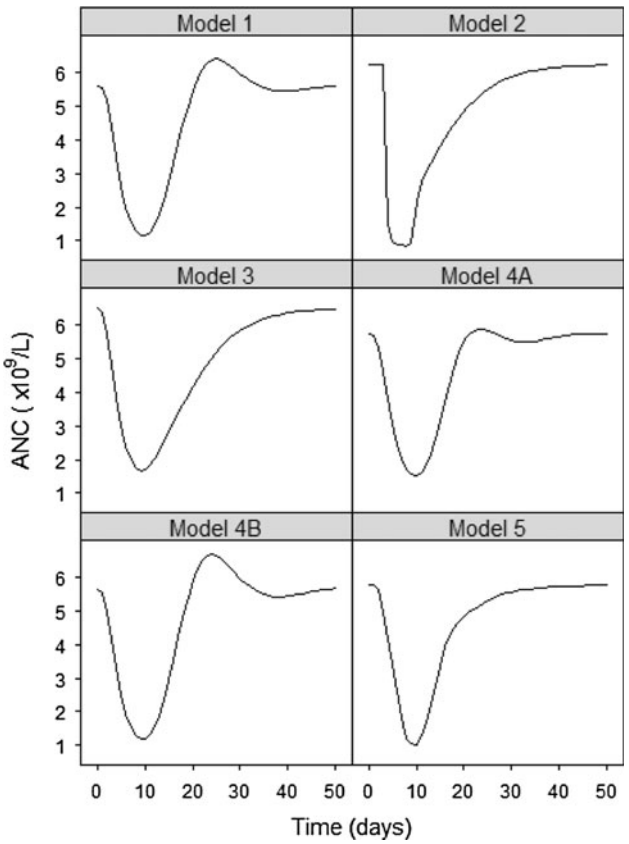

Fig. 2 Typical model-predicted ANC versus time profiles following single administration of 200 mg BI 2536 as 1-h infusion

models. For Model 4A and 4B, IPV in R_{max} was additionally estimated. In the case of Model 1 and 5, data additionally allowed estimation of IPV in MTT and T_P and T_M, respectively. The IPV was low (MTT) to moderate ($Circ_0$) for the system-related parameters and moderate (Model 1 and 4B) to high (Model 2, 3 and 4A) for the drug-related parameters.

The estimate of basal neutrophils in the compartments representing circulating neutrophils was similar in all models (5.62×10^9/l to 6.52×10^9/l) and similar to the median observed value (5.1×10^9/l). The estimates of k_{circ} were similar in Models 1–4. Similar slope values were obtained for Model 4B (0.0277 ml/ng) and Model 1 (0.0196 ml/ng) both of which had the same function for drug effect. These values are similar to that reported previously for BI 2536 [17].

Figure 2 shows the typical model-predicted population ANC profiles following single intravenous infusion of 200 mg BI 2536 for each of the neutropenia models explored. Models 1, 4A and 4B exhibit a rebound effect before recovering the basal ANC. In Model 2, after a very steep initial decrease, ANC stays at levels near to nadir for a longer period of time in comparison with the other models.

Figure 3 shows the PC-VPC for the first three cycles of the treatment including all dosing schedules. All models could adequately describe the median of the observed data, whereas the 10th and the 90th percentiles were not always well captured. In general, for Models 1, 4B and 5, but not in the case of Models 2, 3 and 4A, the lines corresponding to the median and 10th and 90th percentiles of the observations fall inside the area corresponding to the 95% confidence intervals.

The NPC (Fig. 4) show a description of the observed Grade 4 neutropenia (Panel A) and Grade $\geq$3 neutropenia (Panel B) for the first three cycles. The percentage of patients developing Grade 4 neutropenia and Grade $\geq$3 are captured well, and model predictions are similar for Models 1, 4A, 4B and 5. For Models 2 and 3, however, Grade 4 and Grade $\geq$3 toxicities are systematically overpredicted and underpredicted, respectively. Those model discrepancies can have a clinical impact if simulated Grade 4 toxicity is used for dose selection. Efficacy and toxicity will be compromised in the case of using Models 2 and 3, respectively, to simulate next dosing scenarios.

Discussion

Understanding and predicting the haematological adverse events during treatment with cytotoxic drugs has received considerable attention in the population PK/PD area over the last decade. The model developed by Friberg et al. [7] represents the paradigm in semi-mechanistic modelling. In fact, most published population PK/PD modelling analyses dealing with the neutropenic response are based on this model.

With respect to description of the neutropenic response to BI 2536, Model 1, Model 4B and Model 5 described the data well. Model 1 is the most parsimonious. Model 2 and Model 3 described the data significantly worse as shown in the predictive checks. Therefore, the selection of the model published by Friberg et al. [7], as starting point for model development, at least in case of BI 2536, is supported by our analysis.

As it was mentioned previously, Models 2, 3 and 4A fit the data less well. The reason for that result is probably due to the fact that drug effects are limited to exert only an inhibitory effect on cell proliferation, in contrast to the rest of the models where a cell killing process is allowed. The incorporation of a feedback mechanism even in cases where a rebound effect cannot be detected visually might help to better capture the nadir and the recovery. We modified the original Models 2 and 3 by allowing a feedback mechanism. The results indicated better fits but still far from those obtained in Models 1, 4B and 5.

Models 1 and 4B differ in the number of maturation compartments and in the feedback function. Model 4B was

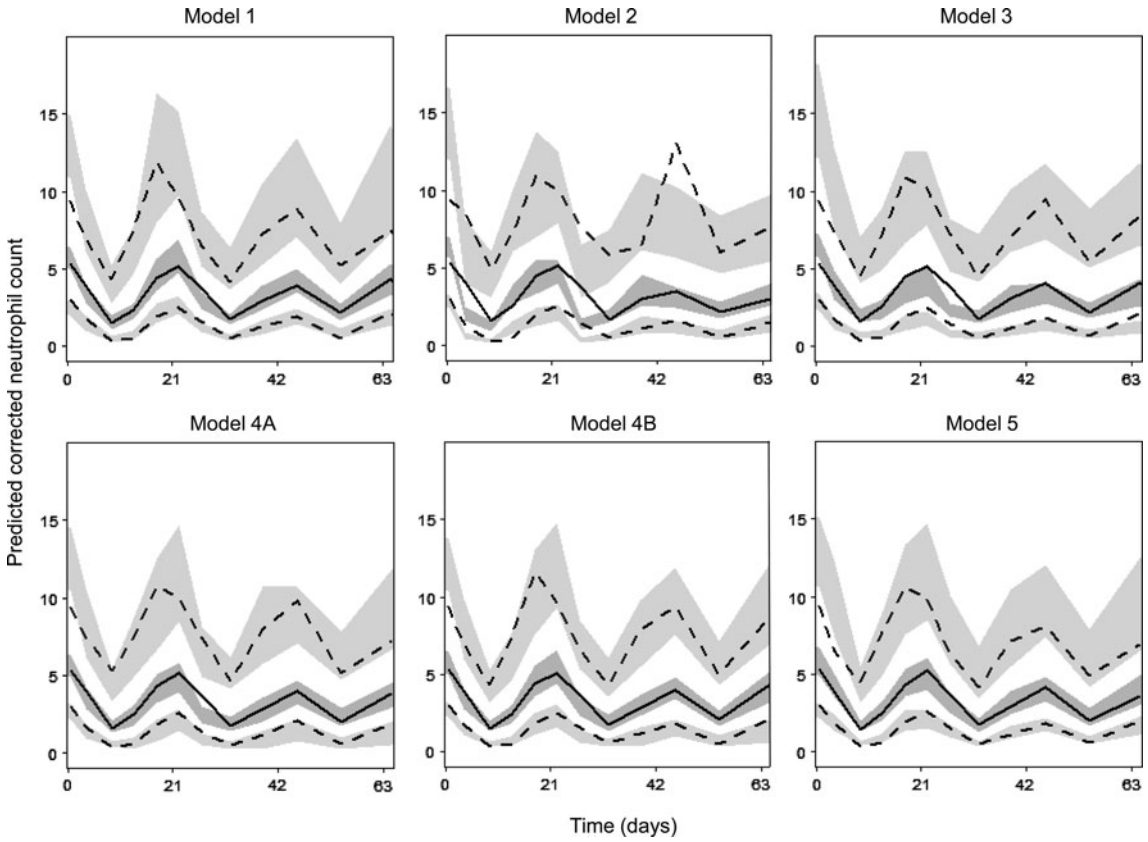

Fig. 3 Prediction-corrected-VPC for ANC versus time after the administration of BI 2536 for Model 1, 2, 3, 4A, 4B and 5. Median (*solid line*), 90th and 10th percentile (*dashed line*) of the observations. *Dark grey areas* cover the 95% CI of the median and *light grey areas* cover the 95% CI of the 90th and the 10th percentiles of the simulated profiles

modified by adding one or two extra maturation compartments. The results obtained indicated that the fit was not improved leading us to conclude that at least for this particular drug and data set, the rebound mechanism is better described by Model 1 despite having one less parameter.

The way drug effect was described differs substantially between the different models. In Models 2, 3 and 4A, BI 2536 acts inhibiting proliferation of progenitor cells, reflecting a cytostatic mode of action, whereas in Model 5, drug behaves as a cytotoxic inducing cell death. In the case of Models 1 and 4B, combination of two mechanisms occurs. Meanwhile the value of E_{DRUG} is ≤ 1, drug inhibits cell proliferation; however, when E_{DRUG} is >1, drug induces cell death. The estimates of the drug effect parameter in Models 1 and 4B were of the same order (0.0196 and 0.0277 ml $\times$ ng^{-1}, respectively).

With respect to the system (drug independent), part of the model differences were located at the level of mechanisms representing (i) proliferation, first-order process (Models 1, 4A and 4B), zero-order process (Models 2, 3 and 5), (ii) maturation/degradation, first-order process (Models 1, 2, 3, 4A and 4B), lifespan (Model 5) and (iii) feedback regulation included in Models 1, 3, 4A and 4B.

Parameters representing the same mechanism had similar values between different models. For example, the values of the first-order rate constant of proliferation ranged between 0.0291 and 0.0385 h^{-1} in Models 1, 4A and 4B. Proliferation described through a zero-order rate process in Models 2 and 3 showed values of 0.214 and 0.195 cell $\times$ h^{-1}, respectively. In the case of Model 5, where the lifespan mechanism was used, the rate of proliferation showed a value of 0.0401 cells $\times$ h^{-1}.

Conceptually, TP + TM and MTT are equivalent. As Bulitta and coauthors have discussed previously [9], the main difference between the two approaches is the distribution assumed for cell lifespans within a patient. As the number of transit compartments increased, the percentiles of the lifespan distribution get closer to the median. In the current case, the lifespan Model did not consider the possibility of estimating different lifespans for cells of the same type within each patient as it has been proposed previously [29].

For Model 5, seventeen differential equations were required, which increased computing time by 20-fold. In the case of more complex pharmacokinetic models or drug combinations, the number of differential equations would

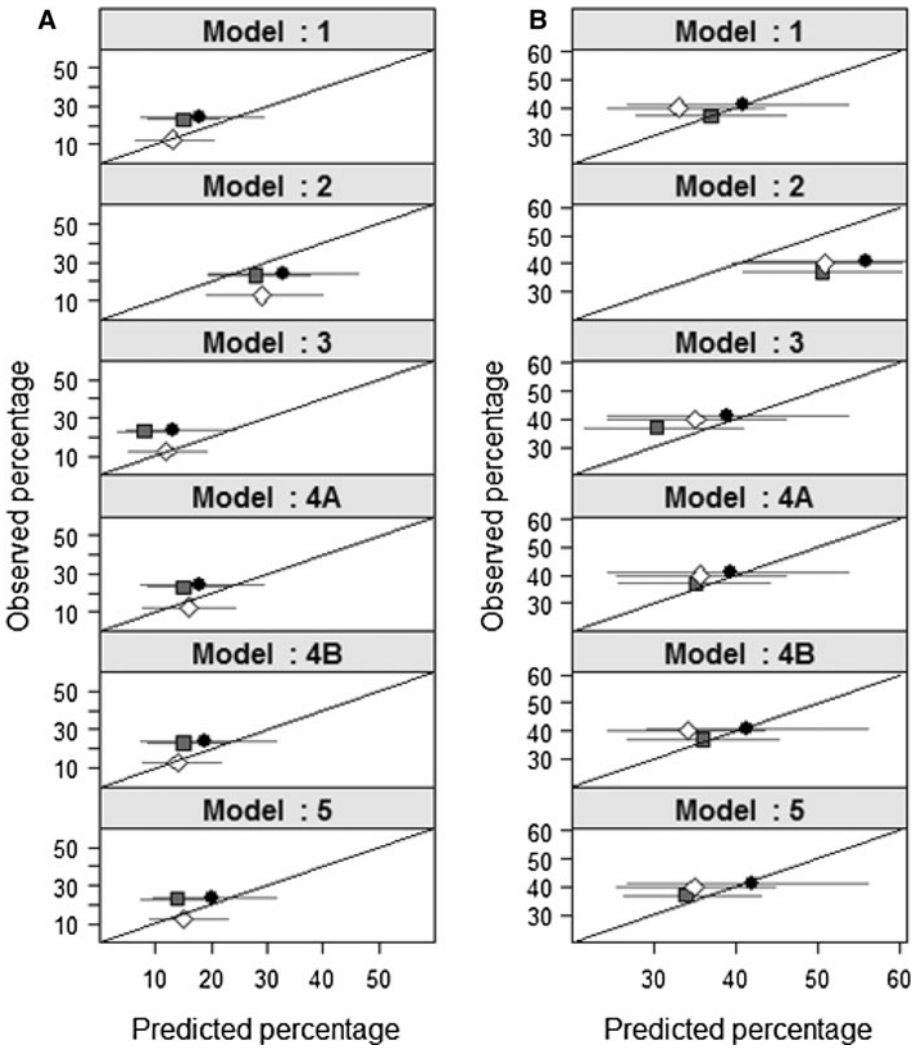

Fig. 4 Relation between the observed and predicted percentage of neutropenia Grade 4 (**a**) or Grade ≥3 (**b**). *Symbols* represent the relation between the observed percentage of patients developing neutropenia (Grade 4 or Grade ≥3) and the overall mean of predicted descriptors for Cycle 1 (*squares*), Cycle 2 (*diamonds*), Cycle 3 (*circles*). *Horizontal lines* represent the 95% prediction interval of the descriptor

increase substantially. Furthermore, standard errors could not be obtained for Model 5 using the covariance step as implemented in NONMEM. It is possible and recommended to obtain parameter precision by applying techniques, such as nonparametric bootstrap, but this alternative is problematic in the case of models associated with very long computing times. One interesting result obtained when fitting Model 5 to our data is that the system-related parameters T_P, T_M and T_N are in the same range to those originally published by Bullita et al. [9]: 196 versus 264 h, 40 versus 47 h and 144 versus 105 h, respectively, indicating that these system parameters are consistent for at least two different drugs. A feedback mechanism that resembles the effects of the G-CSF is not included in Model 5. During this work, it was not possible to implement such a mechanism under the nonlinear mixed effect modelling framework as implemented in NONMEM. Truly delayed differential equations are required for the implementation of this mechanism. The rebound mechanism applied to multiple lifespan models describing the red blood cells kinetics as shown by Ramakrishnan et al. [30], and Woo et al. [31], was not implemented for nonlinear mixed effect modelling.

An additional issue to be considered is the fact that Models 1, 3, 4AB and 5 use drug concentrations to describe drug effects and Model 2 uses AUC. Models in which drug effects are driven by the concentration–time profile are in general preferred over the models using AUC. The former would be more indicated to characterize the presence of complexities in the data, such as schedule dependencies, since different schedules can show same or similar AUC values but very different PK time profiles. From an exploratory point of view, however, relating nadir with AUC could be considered a quick test to detect schedule dependency without the need to model the data.

As only data from a single clinical study investigating the efficacy and safety of BI 2536 in NSCLC were used for this evaluation, the conclusions are basically restricted to

this compound. For a comprehensive comparison, data from different compounds and scenarios (e.g. wide dose range, different dosing schedules) would be needed. All 5 models were implemented in NONMEM. It should be noted that only FOCE method was used during the evaluation and that the new available methods in NONMEM VII were not tried.

This thorough approach would ensure that more options for fitting an adequate model would be explored. However, based on our results, it is likely that the best fit would be derived from Model 1, 4B or 5, and therefore those would be the first models to try, and if model misspecifications are apparent, those models can be expanded or modified. It has to be taken into consideration that in a situation of sparse sampling, the model with less number of parameters (Model 1) appears to be more appropriate. In addition, the system-related parameters can be fixed to the estimates obtained from analyses done with different anticancer drugs and published in literature. This is an advantage of Model 1 over the rest of the models explored. In conclusion, based on the evaluation of the model performance, none of the models was superior to the most commonly applied semi-mechanistic model of neutropenia [7].

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