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ORIGINAL ARTICLE

Limited inter-occasion variability in relation to inter-individual variability in chemotherapy-induced myelosuppression

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Abstract
Purpose A previously developed semi-physiological model of chemotherapy-induced myelosuppression has shown consistent system-related parameter and inter-individual variability (IIV) estimates across drugs. A requirement for dose individualization to be useful is relatively low variability between treatment courses (inter-occasion variability [IOV]) in relation to IIV. The objective of this study was to evaluate and compare magnitudes of IOV and IIV in myelosuppression model parameters across six different anti-cancer drug treatments.
Methods Neutrophil counts from several treatment courses following therapy with docetaxel, paclitaxel, epirubicin-docetaxel, 5-fluorouracil–epirubicin–cyclophosphamide, topotecan, and etoposide were included in the analysis. The myelosuppression model was fitted to the data using NONMEM VI. IOV in the model parameters baseline neutrophil counts (ANC_0), mean transit time through the non-mitotic maturation chain (mean transit time [MTT]), and the parameter describing the concentration–effect relationship (slope), were evaluated for statistical significance ($P < 0.001$).
Results Inter-occasion variability in MTT was significant for all the investigated datasets, except for topotecan, and was of similar magnitude (8–16 CV%). IOV in slope was significant for docetaxel, topotecan, and etoposide (19–39 CV%). For all six investigated datasets, the IOV in myelosuppression parameters was lower than the IIV. There was no indication of systematic shifts in the system- or drug sensitivity-related parameters over time across datasets.
Conclusion This study indicates that the semi-physiological model of chemotherapy-induced myelosuppression has potential to be used for prediction of the time-course of myelosuppression in future courses and is, thereby, a valuable step towards individually tailored anticancer drug therapy.

Keywords Hematologic toxicity · Pharmacodynamics · NONMEM · Inter-occasion variability · Anti-cancer drugs

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Introduction

Traditionally, the initial dose level of most chemotherapeutic agents is based on body surface area (BSA) (mg/m^2). In spite of this attempt for dose individualization, toxicity and efficacy vary considerable among patients [1] where myelosuppression is the most common and often dose-limiting adverse event [2]. For patients with unacceptable toxicity, the next dose is generally reduced in more or less crude predefined steps and/or the treatment interval is prolonged, whereas when little or no toxicity is observed, dose escalations are seldom performed outside clinical trials. Consequently, patients may experience suboptimal tumor effects as low dose intensity and/or lack of hematological toxicity is associated with shorter survival [3–6].

In an optimal dosing strategy, the desired antitumoral effects have to be carefully balanced against the side effects for each individual. A way to do this could be to use the observed neutrophil counts from one treatment cycle as a base for dose adjustment in the next cycle. A model-based tool for efficient dose individualization based on neutrophil counts has recently been developed [7]. This tool uses a maximum a posteriori (Bayesian) approach to calculate a suitable dose for the next course based on a previously developed population pharmacokinetic–pharmacodynamic model for chemotherapy-induced myelosuppression [8] and observed neutrophil counts. The value of the dose-individualization tool depends on relatively low variability between treatment courses, inter-occasion variability (IOV), in myelosuppression model parameters in relation to the inter-individual variability (IIV), i.e., to which extent the observed neutrophil counts are predictable at the next course within the same patient.

A semi-physiological model that describes the magnitude and duration of myelosuppression following anticancer treatment has previously been developed [8]. The model (Fig. 1) is composed of five compartments, which imitate the myelopoiesis. One compartment represents proliferating cells in the bone marrow and is linked via three transit compartments, mimicking cell maturation, to a compartment corresponding to circulating observed neutrophils. Included is also a feedback mechanism increasing the neutrophil production when the number of circulating neutrophils in the blood are reduced representing, e.g., the action of endogenous granulocyte colony stimulating factor (G-CSF). The drug is assumed to act by inhibiting the proliferation rate and inducing cell loss. In most cases, it is sufficient to use a single parameter related to the drug concentration–effect relationship, i.e., a linear drug effect parameter (slope). The estimated parameters associated to the hematopoietic system are the baseline neutrophil count (ANC_0), the mean transit time through the maturation chain (mean transit time [MTT]), and the feedback factor gamma (γ).

The semi-physiological myelosuppression model has found applications in many areas of drug development and has previously been applied to several different anticancer drug therapies, see for example [9–16]. Consistency in the system-related parameter estimates and in the magnitude of IIV in the parameters across drugs have been reported [8]. However, there is limited information on the within-individual variability between courses (IOV) in the estimated parameters. The aim of the present study was to evaluate IOV in myelosuppression model parameters and compare their magnitudes with IIV estimates across six different treatments to assess the semi-physiological model's potential as a tool for individual dose adjustments based on observed neutrophil counts.

Patients and methods

Patients and treatment

Neutrophil counts from several treatment courses were available following therapy with docetaxel, paclitaxel, epirubicin–docetaxel (ET), 5-fluorouracil–epirubicin–cyclophosphamide (FEC), topotecan, and etoposide. Data from treatment cycles, where patients were known to have received G-CSF therapy, were excluded from the analysis. All patients signed informed consent forms and the studies were in accordance with the Declaration of Helsinki and approved by local ethics committees. A summary of the analyzed datasets, number of patients, number of treatment cycles per patients, number of available neutrophil observations, and number of neutrophil observations per patient and treatment cycle is presented in Table 1.

Docetaxel

Neutrophil counts from 244 metastatic breast cancer patients treated with docetaxel were included in the

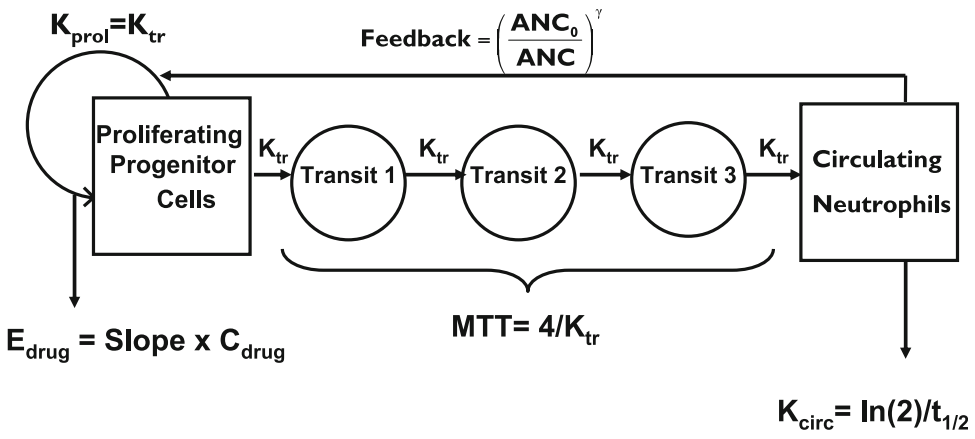

Fig. 1 The semi-physiological model of myelosuppression with the system-related model parameters (ANC_0), mean transit time (MTT), feedback factor γ, and the drug–effect parameter (slope). K_{tr}, proliferation rate constant; K_{circ}, elimination rate constant for circulating neutrophils; $(ANC_0/ANC)^{\gamma}$ feedback loop from the circulating neutrophils

Table 1 Data summary of the analyzed datasets

Dataset	Patients (*n*)	Cycles/patient median (range) (*n*)	Neutrophil observations (*n*)	Neutrophil observations/patient and cycle median (range) (*n*)
Docetaxel	244	4 (1–16)	2,262	1.6 (1.1–3.2)
Paclitaxel[a]	45	3 (1–11)	523	2.6 (0.9–3.5)
Epirubicin–docetaxel	41	4 (1–9)	659	3.6 (2.9–4.7)
5-Fluorouracil–epirubicin–cyclophosphamide	60	7 (2–10)	1,196	3.4 (1.7–4.4)
Topotecan	26	2 (1–8)	501	6.0 (5.5–8.8)
Etoposide	44	2 (2–2)	583	6.3 (5.6–7.1)

[a] Data from 11 out of 18 treatment cycles were analyzed as only one individual contributed >11 cycles

analysis [17]. The patients were part of the active control group in a clinical trial studying the combination treatment of capecitabine and docetaxel. Initial dose level was 100 mg/m^2 of docetaxel administered as a 1-h intravenous infusion in a 3-week cycle. Dose reductions were based on hematological and non-hematological toxicity and resulted in a final dose range of 50–100 mg/m^2.

Paclitaxel

The paclitaxel data included neutrophil counts from 45 patients with different cancer forms [18]. Paclitaxel was administered as a 3-h infusion with an initial dose of 175 mg/m^2 every third week. Doses were adjusted based on hematological and non-hematological toxicity resulting in a final dose range of 110–232 mg/m^2.

Epirubicin–docetaxel

The ET dataset included 41 advanced breast cancer patients [15]. Epirubicin was given in a 3-week cycle as a 1-h infusion followed by a 1-h free interval and then a 1-h infusion of docetaxel. Initial doses were 75/70 mg/m^2 with escalated/reduced doses in the following cycles based on leukocyte and platelet counts according to the study protocol.

5-Fluorouracil–epirubicin–cyclophosphamide

Sixty breast cancer patients treated with either standard or tailored FEC regimen were included in the analysis [14]. The treatment was administered every third week as a 15-min infusion of cyclophoshamide followed by 5-fluorouracil given as an intravenous bolus dose and epirubicin given either as a bolus or as a 1-h infusion. The initial doses of 5-fluorouracil, epirubicin, and cyclophosphamide were in the first treatment cycle for standard FEC 600/60/600 mg/m^2, respectively, and for the tailored therapy 600/75/900 mg/m^2, respectively. Subsequent doses were reduced based on toxicity in the standard therapy and in the tailored therapy doses were stepwise escalated or decreased based on the observed nadir and the dosing day leukocyte/platelet count according to a dose escalation/reduction protocol.

Topotecan

Data from 26 patients with various types of solid tumors treated with topotecan as single anticancer drug therapy were included in the analysis [19]. Initial dose level was 6 mg/m^2 administered as a 24-h intravenous infusion every third week. No dose adjustments were performed according to the study protocol.

Etoposide

Data from 44 patients with solid tumors and hematological malignancies who received two treatment courses of a 3-day continuous infusion of etoposide in a 28 day cycle were analyzed [20, 21]. The patients were randomized to either standard dosing with a total dose of 375 mg/m^2 or concentration guided dosing where the total delivered dose ranged from 225–789 mg/m^2 following dose adjustments.

Data analysis

To describe the pharmacokinetics (PK) and pharmacodynamics (PD) following single-agent or combined chemotherapy non-linear mixed effects modeling was applied using the first-order conditional estimation (FOCE) method in NONMEM version VI [22]. The non-linear mixed effects modeling approach estimates the typical (mean) value of parameters and can provide separate estimates of IIV, IOV, and residual error variability.

The model building process was guided by graphical diagnostics within the R-based software Xpose version 4.0 [23] (http://xpose.sourgeforge.net), and the change in objective function value (OFV) computed by NONMEM was judged by the likelihood ratio test. For two nested models, the difference in OFV is equal to minus twice the

log likelihood and approximately χ^2 distributed. A difference in OFV of >10.83 corresponds to a significance level of $P < 0.001$ for one additional parameter.

Pharmacokinetics

For the docetaxel dataset, no individual PK data were available and typical population PK parameters were used to describe the concentration–time profiles of the drug [24]. The PK of paclitaxel (average 3.5 PK samples per patient from treatment course 1 and 3) was described using individual PK parameters from a previously determined PK model for the dataset [18]. On average 4.5 PK samples per patient at 18 occasions from 16 patients were used to describe the PK of ET using individual PK parameters from a previous PK model for the ET dataset (12). For the FEC dataset, concentration–time profiles were obtained using doses and individual PK parameters (22% of the patients, 2–7 samples per patient) or typical population parameters when no PK information was available (78% of the patients) from a previously developed PK model [14].

The individual concentration–time course of topotecan and etoposide were derived from observed plasma concentrations and PK models developed by Legér et al. [25] and Toffoli et al. [26], respectively. For etoposide, two plasma concentration samples per patient and treatment course were sampled [19], and for topotecan, 185 plasma concentration measurements of total topotecan were obtained in the first treatment course [20, 21].

When pharmacokinetic observations were lacking and population typical values were used in describing the PK of the drugs, all IIV were assumed to be in myelosuppression and will likely result in an inflated IIV in the slope parameter.

Pharmacodynamic modeling of myelosuppression

The semi-physiological model of myelosuppression was fitted to the neutrophil data. The model structure was the same as in the original publication [8] except that the half-life of circulating neutrophils was fixed to the literature value of 7 h [27] and the neutrophil data were Box-Cox transformed ($ANC_{transformed} = (ANC^{\lambda}-1)/\lambda$) with $\lambda = 0.2$ prior to the analysis as this transformation resulted in residuals with a symmetrical distribution around zero [28, 29].

The subroutine PRIOR within NONMEM [22, 30] was used to be able to estimate separate drug effect parameters (slope) for the co-administered drugs in the ET and FEC regimens. The prior information was incorporated as a frequentist prior where a penalty is added to the objective function on deviation from the prior. The estimated slope parameter for docetaxel (typical value and standard error) in the single drug dataset was used as informative prior for the docetaxel drug effect parameter when analyzing the ET dataset. The obtained population estimate and standard error of the epirubicin slope parameter in the ET regimen was, thereafter, used as prior when modeling FEC. The drug effects were assumed to be additive as this assumption has previously been shown to be reasonable for leukocytes [14, 15].

The random IIV and IOV were modeled in terms of eta (η) and kappa (κ) variables, respectively [31]. The ηs and κs were assumed to be log-normally distributed parameters both with mean zero and variances ω^2 and π^2, respectively. The IIV and IOV variance parameters were constant across all occasions. The random residual error, the differences between the observed neutrophil count and the model predicted neutrophil count, was modeled as an additive component (on Box-Cox scale).

As in the original publication of the semi-physiological model of myelosuppression [8], IIV was included for the model parameters ANC_0, MTT, and slope for all datasets. IOV was evaluated for statistical significance ($P < 0.001$) using OFV in the likelihood ratio test for ANC_0, MTT, and slope. One occasion was defined as one treatment course with the nominal cycle length of 21 or 28 (etoposide) days. To exclude the possibility of time-dependent and non-random variability between occasion's linear changes with time in ANC_0, MTT and slope were estimated and evaluated for statistical significance ($P < 0.001$). Time-dependent changes in the model fit were also evaluated by graphical assessment of the conditional weighted residuals (CWRES).

Reliability in the parameter estimates were determined by standard errors obtained from the S matrix (R matrix for topotecan) in NONMEM due to long run times and as these standard errors are good approximations to the standard errors obtained by the NONMEM default sandwich matrix and to a non-parametric bootstrap procedure [32].

The predictive performance of the final models (including IOV) for the different treatment regimes was assessed by applying a visual predictive check [33]. The median and the 10th and 90th percentiles of the prediction intervals were derived from 1,000 simulated replicates of the dataset using the final model parameter estimates. The computed prediction intervals and the percentiles of the observed data were plotted versus time to allow comparison of the predictions with observations. To assess the expected uncertainty in the median and the 10th and 90th percentiles (arising, e.g., from the design), 95% confidence intervals were calculated from the simulated datasets.

The contribution of IOV in the myelosuppression model parameters to the variability in nadir in relation to the IIV was explored by comparison of the distribution of simulated nadir counts. The final population parameter

estimates for each of the six analyzed datasets were used to simulate 1,000 time-courses of myelosuppression for all treatment regimes in three different scenarios: (i) including only the estimated IIV, (ii) including only the estimated IOV, and (iii) including both the estimated IOV and the IIV. The nadirs for the 1,000 simulated time-courses were identified and the distributions of simulated nadir counts, including only IIV, only IOV, or both IOV and IIV, were compared.

Results

The myelosuppression model could well characterize the neutrophil–time course following both the single-agent and combination therapy for all the investigated datasets and resulted in similar system-related parameter estimates as previously observed for other datasets [8, 34]. For 5-fluorouracil, slope was not significantly different from zero, i.e., the drug effect for 5-fluorouracil could not be separated from the drug effect of epirubicin and cyclophosphamide with the present data (Table 2).

The VPCs of the semi-physiological myelosuppression models for the six different treatment regimes are presented in Fig. 2 and shows that the models describe the data adequately.

Estimated IIV and IOV in the model parameters and the decrease in residual errors after IOV inclusion are reported in Table 2. In accordance with previous results [8, 34], IIV in the ANC_0 and slope parameters were larger than IIV in MTT. IIV in ANC_0 was similar across drugs (slightly higher for etoposide) while the IIV in slope varied (22–62 CV%) between different treatments. The IIV in slope was lower in the drug combination datasets (where a common IIV parameter for slope was estimated for the component drugs) compared to the single agent data. IIV in slope for topotecan was estimated to be relatively high compared with the other investigated datasets.

Inter-occasion variability in MTT was significant and of similar magnitude (7.5–16 CV%) for all the investigated datasets, except for topotecan where only IOV in slope was significant to include. IOV in slope was also found to be significant for docetaxel and etoposide. By inclusion of IOV in the myelosuppression model parameters, the residual errors decreased on average 21% for all datasets with the highest decrease in residual errors observed for the paclitaxel and etoposide datasets (Table 2).

There were no significant time-dependent changes in parameters, where IOV was included indicating that the estimated κs, were random and not time dependent. Significant linear trends over time were, however, found in ANC_0 for the FEC and etoposide datasets for which IOV were not significant in ANC_0. The estimated trend over time corresponds to a decrease in ANC_0 from 4.56 to 3.81×10^9/l neutrophils 15 weeks after first treatment for the typical patient treated with FEC. For etoposide, an increase in ANC_0 from 5.69 to 6.32×10^9/l neutrophils was estimated 4 weeks after first treatment. No time-dependent changes in the model fit (Fig. 3) were visible in the graphical assessment of CWRES.

η-Shrinkage for IOV was in general high and ranged from 12 to 95% and was for IIV generally lower and ranged from 6 to 48%. The high shrinkage values indicated that goodness-of-fit plots based on empirical Bayes estimates were not reliable for model evaluation, and therefore, CWRES and simulation based methods were used.

In all six datasets, the contribution to the variability in neutrophil nadir was clearly lower from IOV than from IIV as shown in Fig. 4a. The impact of the estimated IIV and IOV on the time-courses of myelosuppression is visualized in Fig. 4b for 20 simulated individuals.

Discussion

The time-course of neutrophils following chemotherapy is here described for six different anti-cancer drug treatments for which the estimated parameters are reported. The semi-physiological myelosuppression model has not previously been applied for neutrophils for the here used datasets on docetaxel, ET, FEC, and topotecan, and for none of the datasets has IOV previously been characterized. For all six investigated dataset, the impact of IOV on the variability in nadir counts was lower in relation to the IIV (Fig. 4a).

The model accurately describes the time-course of myelosuppression following all treatments as shown in the visual predictive checks (Fig. 2) and no indications of model misspecifications are present. However, if higher doses of the anticancer drugs are administered a different model for the drug effect might be needed to be considered, e.g., an E_{max} or sigmoidal E_{max} model to accurately reflect the myelosuppression.

Typically IIV parameters were of similar magnitudes across drugs but the estimated IIV in slope for topotecan was high (62%), which may be explained by a heterogeneous patient population with advanced disease. The estimate of the system-related parameter ANC_0 for topotecan (7.1×10^9/l) was also higher than for the other investigated dataset in the current and previous studies [8] but was in accordance with the observed initial baseline neutrophil count, 6.8×10^9/l.

Inter-occasion variability in MTT was significant for all the investigated datasets except for topotecan. This may indicate that MTT is a parameter, which influences most of the neutrophil observations and therefore inclusion of IOV in MTT results in a significant improvement of the fit.

Table 2 Typical population parameter estimates (relative SE %) for final models including IOV

Dataset	ANC_0 ($\times 10^9$/l)	MTT (h)	Slope 1 (μM^{-1})	Slope 2 (μM^{-1})	γ	Residual error[a]	
Docetaxel	4.81 (2.6)	94.0 (1.6)	17.3 (3.4)	–	0.170 (1.8)	0.528 (1.1)	
Paclitaxel	5.61 (9.4)	154 (4.4)	69.6 (8.1)	–	0.270 (5.9)	0.431 (2.6)	
Epirubicin–docetaxel	3.49 (11)	117 (3.1)	17.8 (32)[b]	17.4 (29)[c]	0.207 (5.1)	0.499 (3.4)	
5-Fluorouracil–epirubicin–cyclophosphamide[e]	4.56 (5.3)	184 (3.2)	32.2 (47)[b]	26.6 (22)[d]	0.241 (2.4)	0.535 (1.9)	
Topotecan	7.11 (9.6)	157 (5.6)	0.0370 (27)	–	0.275 (8.6)	0.472 (1.1)	
Etoposide	5.69 (9.8)	162 (6.9)	0.128 (11)	–	0.170 (3.4)	0.492 (4.5)	
	IIV ANC_0 (CV%)	IIV MTT (CV%)	IIV slope (CV%)	IOV ANC_0 (CV%)	IOV MTT (CV%)	IOV slope (CV%)	Δ Residual error (%)
Docetaxel	33 (5.9)	9.0 (19)	37 (7.0)	–	16 (4.8)	19 (12)	−17
Paclitaxel	36 (13)	17 (22)	39 (20)	–	16 (8.5)	–	−41
Epirubicin–docetaxel	37 (15)	12 (21)	22 (23)[f]	–	8.0 (20)	–	−17
5-Fluorouracil–epirubicin–cyclophosphamide	28 (15)	16 (13)	23 (14)[f]	–	7.5 (11)	–	−7.0
Topotecan	32 (27)	15 (34)	62 (45)	–	–	28 (39)	−3.3
Etoposide	47 (15)	23 (24)	28 (42)	–	12 (39)	39 (24)	−38

Δ Residual error is the relative change in residual error after inclusion of IOV

[a] On Box-Cox transformed scale

[b] Epirubicin

[c] Docetaxel

[d] Cyclophosphamide

[e] Slope for 5-fluorouracil not significantly different from zero

[f] Common IIV parameter for slope for the component drugs

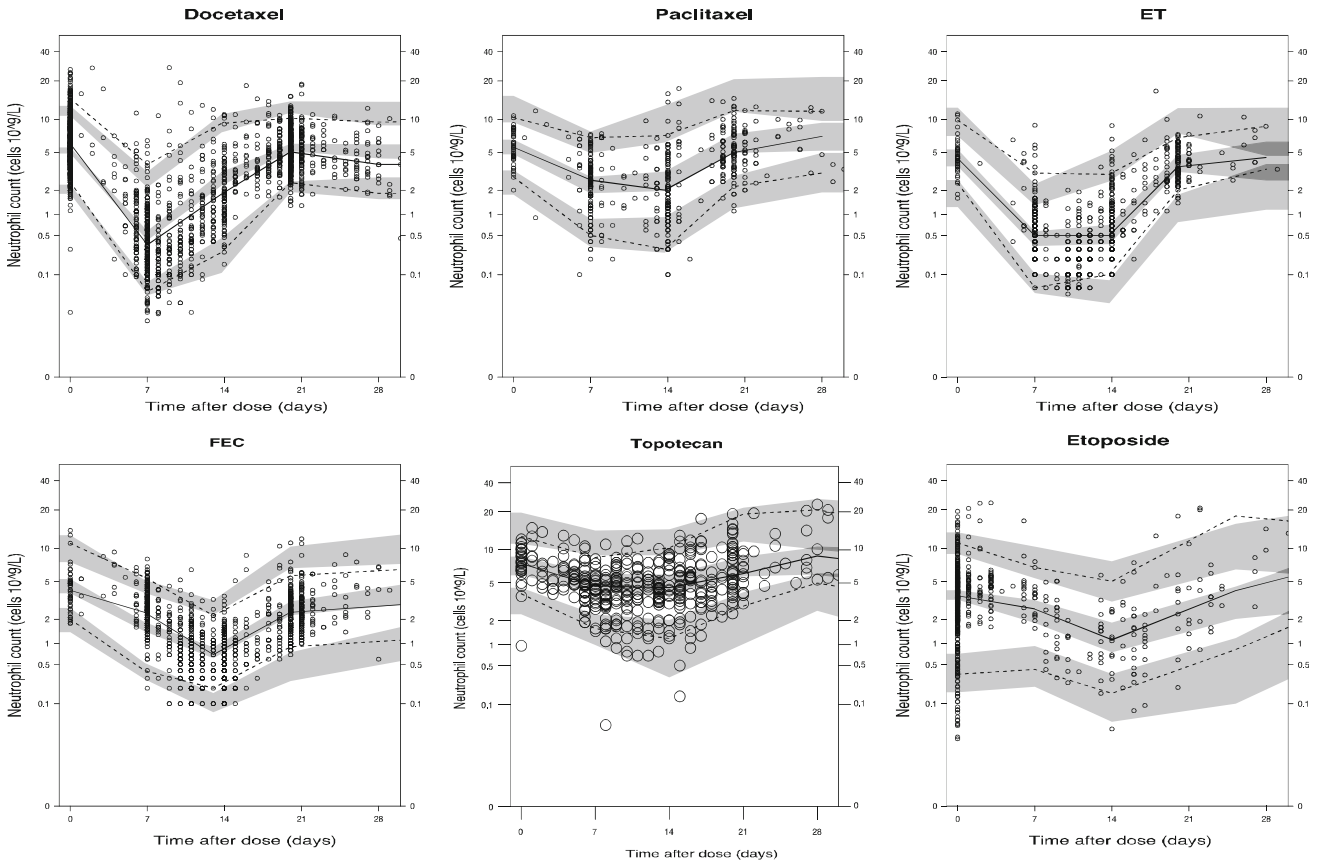

Fig. 2 Visual predictive checks of the final semi-physiological myelosuppression models. The *circles* represent observed data, the *solid line* the median of the observed data and the *dashed lines* the 10th and 90th percentiles of the observed data. *Gray shaded areas* are the confidence intervals based on the simulated data's 10th, 50th, and 90th percentile

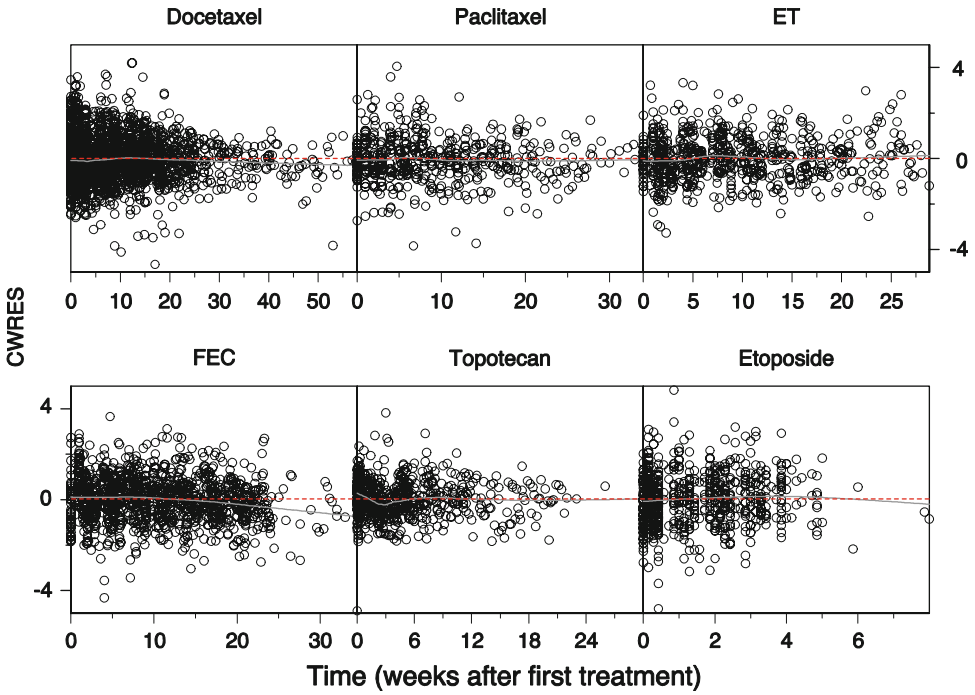

Fig. 3 Graphical evaluation of time-dependent changes in the model fit by conditional weighted residuals (CWRES) versus time for the six investigated datasets

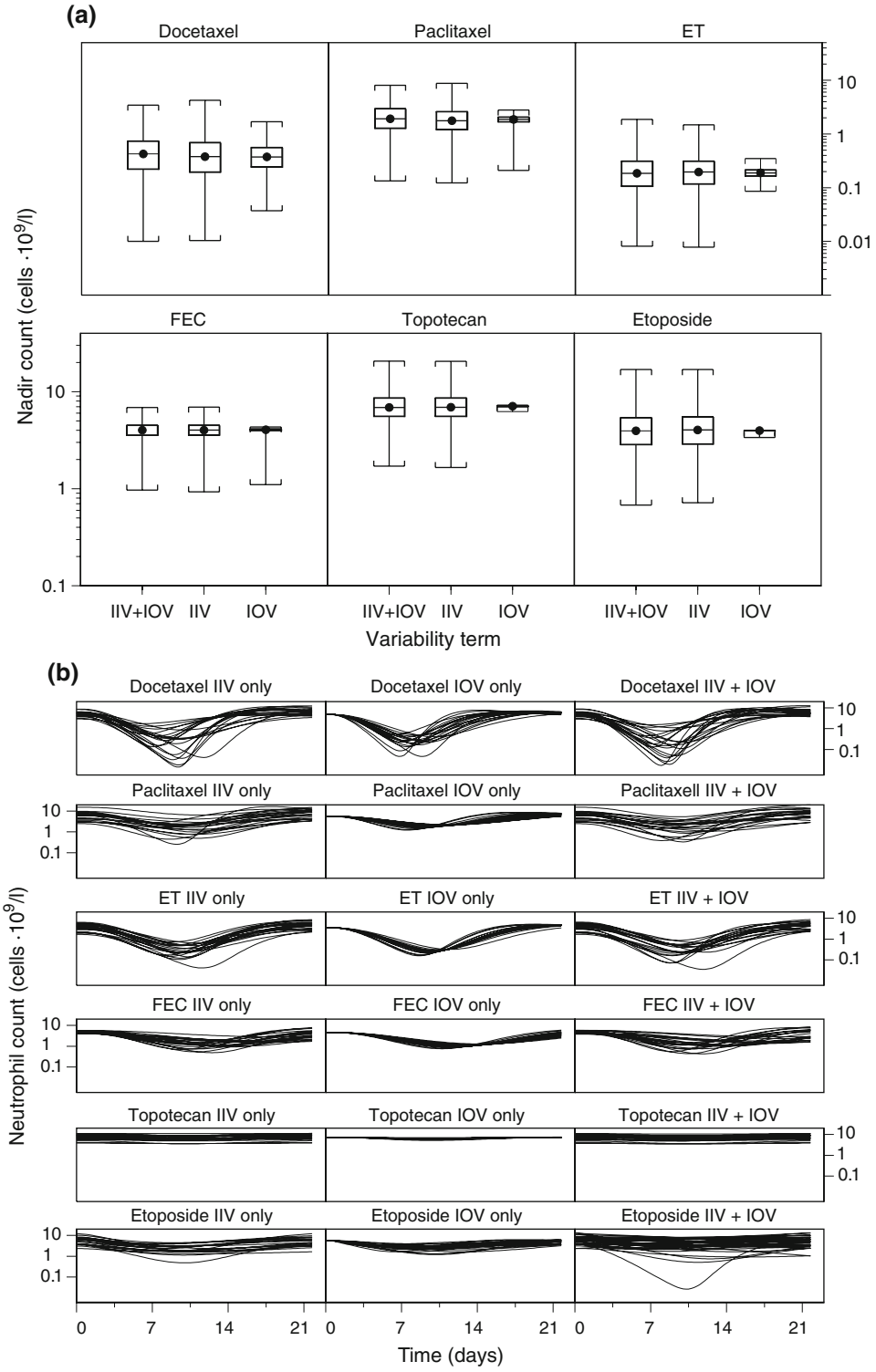

Fig. 4 **a** Box-plots of simulated nadir distributions for all six treatment regimens including both IOV and IIV, only IIV, or only IOV to illustrate the contribution of IOV and IIV to the variability in nadir. The *solid circle* corresponds to the median, the top and bottom of the box, the 25th and 75th percentiles, and the whiskers to the maximum and minimum of the simulated nadir counts. **b** Twenty simulated individual time-courses of myelosuppression including IIV only, IOV only, or IIV and IOV for all the six investigated datasets

Potential variability between treatment courses in drug sensitivity and baseline neutrophil count within an individual appeared, however, of lower importance.

For none of the datasets did the drug sensitivity of the bone marrow increase with time and typically potential changes in pre-treatment neutrophil counts over time were predicted by the model. Significant linear changes with time in ANC_0 were, however, found for FEC and etoposide, but the observed trends were of small magnitudes and in opposite directions. A decrease in ANC_0 over time was observed for FEC in contrast to an increase over time for etoposide. As no time-dependent trends were observed in

any of the other investigated datasets, it is hard to draw any conclusion from the findings.

Inter-occasion variability in myelosuppression model parameters for oral and intravenous administered topotecan as mono therapy or in combination with cisplatin have been reported previously by Léger et al. [11]. The estimated IOV in slope and MTT were 93 and 22%, respectively. A part of the large IOV in slope was speculated to be caused by the oral administration route and the different treatment sequences of topotecan and cisplatin between cycle 1 and 2. In our analysis, only IOV in slope (29 CV%) was found significant for topotecan, whereas IOV in MTT was not supported by the data. In the Léger study, the first-order estimation method was used and the estimated variability parameters were associated with large confidence intervals and thus there may not be a conflict between their findings and ours. For both studies on topotecan, the estimated IOV in relation to the IIV was lower.

Pharmacokinetics was not determined in all treatment cycles in any of the analyzed datasets and, therefore, potential IOV in PK was likely incorporated in residual error estimates or in IOV of the myelosuppression model parameters. IOV in pharmacokinetic parameters for the component drugs of the ET, FEC, and topotecan regimens has earlier been shown to be limited and less than the IIV [11, 14, 15].The estimated IOV in clearance ranged between 14 and 18%.

Two alternative a posteriori dosing strategies to traditional dose adjustments in predefined steps are pharmacokinetic and pharmacodynamic adaptive control [35]. The adaptive control strategies have been successfully evaluated in the clinic for some antineoplastic agents [36, 37]. However, except for methotrexate, these dose–adaptation methods have not found widespread use with the primary reason being the poorly defined relationship between plasma drug concentrations, therapeutic effect, and/or toxicity. Neither has the suggested dosing strategies (except for methotrexate) yet prospectively proved benefit in terms of increased response and reduced toxicity [36, 37]. By using the semi-physiological myelosuppression model [8] as a tool for dose individualization based on observed neutrophil counts, both individual pharmacokinetic and pharmacodynamic differences between patients may be accounted for and doses can be tailored to acceptable neutropenia.

In conclusion, for all six investigated datasets of chemotherapy-induced myelosuppression, the estimated impact of IOV in myelosuppression parameters on the variability in nadir counts was clearly lower than the IIV. No indication of systematic shifts in the system- or drug sensitivity-related parameters over time across datasets was present. The time-course of myelosuppression is thereby shown to be predictable within a patient, which supports the use of the recently developed model-based dose individualization tool based on observed neutrophil counts [7]. This study is, thus, a valuable step towards individually tailored anticancer drug therapy when myelosuppression is dose-limiting.

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Conflict of interest statement None.

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