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 (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 (MTT) and the parameter describing the concentration-effect relationship (Slope) were evaluated for statistical significance ($P < 0.001$).

Results: IOV 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 data sets.

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*

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 since a 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 (MTT) and the feedback factor gamma (γ).

The semi-physiological myelosuppression model has been applied to several different anticancer drugs and found applications in many areas of drug development [9]. 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.

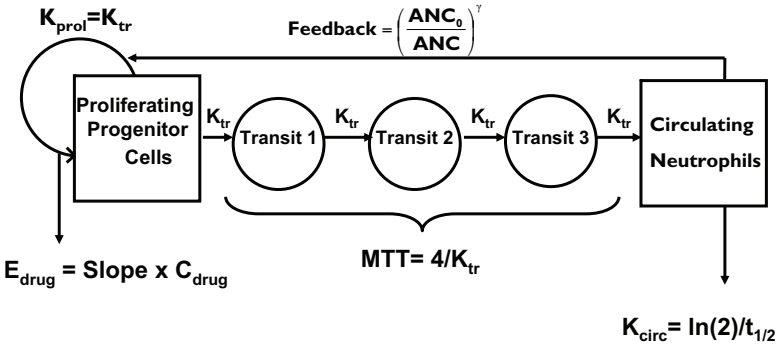

Fig. 1 The semi-physiological model of myelosuppression with the system related model parameters (ANC_0), mean transit time (MTT), feedback factor γ and the drug-effect parameter (Slope). K_{tr}, proliferation rate constant; K_{circ}, elimination rate constant for circulating neutrophils; $(ANC_0/ANC)^{\gamma}$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

Patients and Methods

Patients and treatment

Neutrophil counts from several treatment courses were available following therapy with docetaxel, paclitaxel, epirubicin-docetaxel, 5-fluorouracil-epirubicin-cyclophosphamide, topotecan and etoposide. Data from treatment cycles where patients were known to have received granulocyte colony stimulating factor (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 analysis [10]. 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-hour 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.

Table 1. Data summary of the analyzed data sets

Data set	n patients	n cycles/ patient median (range)	n neutrophil observations	n neutrophil observations /patient & cycle median (range)
Docetaxel	244	4 (1-16)	2262	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)	1196	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.

Paclitaxel

The paclitaxel data included neutrophil counts from 45 patients with different cancer forms [11]. Paclitaxel was administered as a 3-hour infusion with an initial dose of 175 mg/m^2 every 3rd 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 epirubicin-docetaxel (ET) dataset included 41 advanced breast cancer patients [12]. Epirubicin was given in a 3-week cycle as a 1-hour infusion followed by a 1-hour free interval and then a 1-hour 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 5-fluorouracil-epirubicin-cyclophosphamide (FEC) regimen were included in the analysis [13]. The treatment was administered every 3rd week as a 15 minute infusion of cyclophoshamide followed by 5- fluorouracil given as an intravenous bolus dose and epirubicin given either as a bolus or as a 1-hour 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 [14]. Initial dose level was 6 mg/m^2 administered as a 24-hour intravenous infusion every 3rd 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 [15, 16]. 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 [17]. This approach estimates the typical (mean) value of parameters and can provide separate estimates of inter-individual (IIV), inter-occasion (IOV) and residual error variability.

The model building process was guided by graphical diagnostics within the R-based software Xpose version 4.0 [18] (http://xpose.sourgeforge.net) and the change in objective function value (OFV) computed by NONMEM in the likelihood ratio test. For two nested models the differences 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 data set no individual PK data were available and typical population PK parameters were used to describe the concentration-time profiles of the drug [19]. 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 data set [11]. 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 [13].

The individual concentration-time-course of topotecan and etoposide were derived from observed plasma concentrations and PK models developed by Legér et al. [20] and Toffoli et al. [21], respectively. For etoposide two plasma concentration samples per patient and treatment course were sampled [14] and for topotecan 185 plasma concentration measurements of total topotecan were obtained in the first treatment course [15, 16].

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 hours [22] and the neutrophil data were Box-Cox transformed ($ANC_{transformed} = (ANC^{\lambda}-1)/\lambda$) with λ=0.2 prior to the analysis as this transformation resulted in residuals with a symmetrical distribution around zero [23, 24].

The subroutine PRIOR within NONMEM [17, 25] 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 data set was used as informative prior for the docetaxel drug effect parameter when analyzing the ET data set. 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 [12].

The random IIV and IOV were modeled in terms of eta (η) and kappa ($\varkappa$) variables, respectively [26]. The ηs and $\varkappa$s were assumed to be log-normally distributed parameters both with mean zero and variances ω^2 and π^2, respectively. The IOV and IIV 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 com-

ponent (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 in NONMEM default sandwich matrix and to a non-parametric bootstrap procedure [27].

The magnitude of IOV in the myelosuppression model parameters in relation to the IIV was explored by comparison of the variability in simulated nadir counts. The final parameter estimates for each of the six analyzed data sets were used to simulate 1000 time-courses of myelosuppression for all treatment regimes including only IIV, only IOV, or both IOV and IIV. The nadirs for the 1000 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 data sets [8, 28]. 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).

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, 28] 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 the different treatments. The IIV in Slope was lower in the drug combination data sets (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.

IOV 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 data sets 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

Table 2. Typical population parameter estimates (relative SE %) for final models including IOV. Δ residual error is the relative change in residual error after inclusion of IOV.

Data set	ANC_0 (x 10^9/L)	MTT (hours)	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)	[b]17.8 (32)	[c]17.4 (29)	0.207 (5.1)	0.499 (3.4)	
[e]5-Fluorouracil-epirubicin-cyclophosphamide	4.56 (5.3)	184 (3.2)	[b]32.2 (47)	[d]26.6 (22)	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)	[f]22 (23)	-	8.0 (20)	-	- 17
5-Fluorouracil-epirubicin-cyclophosphamide	28 (15)	16 (13)	[f]23 (14)	-	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

[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

IOV was included indicating that the estimated $\varkappa$s 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 x 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 x 10^9/L neutrophils was estimated 4 weeks after first treatment. No time-dependent changes in the model fit (Figure 2) were visible in the graphical assessment of CWRES.

In all six data sets, the contribution to the variability in neutrophil nadir was clearly lower from IOV than from IIV as shown in Figure 3. The impact of the estimated IIV and IOV on the time-courses of myelosuppression is visualized in Figure 4 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 data sets on docetaxel, ET, FEC and topotecan, and for none of the data sets 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.

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 x 10^9/L) was also higher

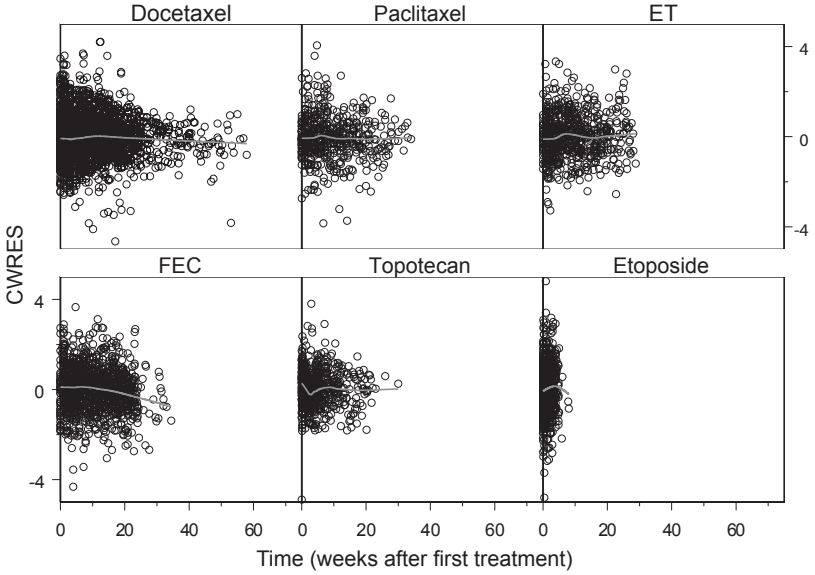

Fig. 2 Graphical evaluation of time-dependent changes in the model fit by conditional weighted residuals (CWRES) versus time for the six investigated datasets.

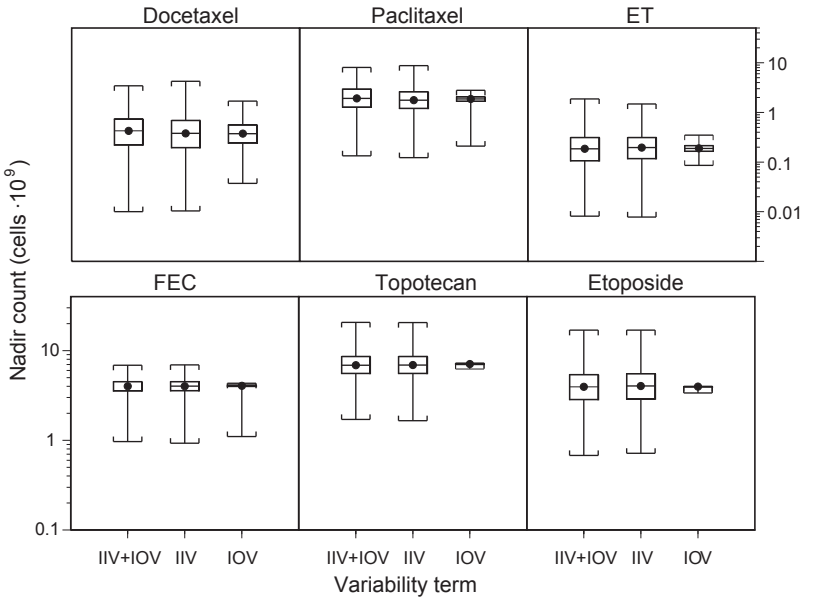

Fig. 3 Box-plots of simulated nadir distributions for all six treatment regimens including both IOV and IIV, only IIV or only IOV. The solid circle corresponds to the median, the top and bottom of the box the 25th and 75th percentiles and the whiskers to the maximum and minimum of the simulated nadir counts

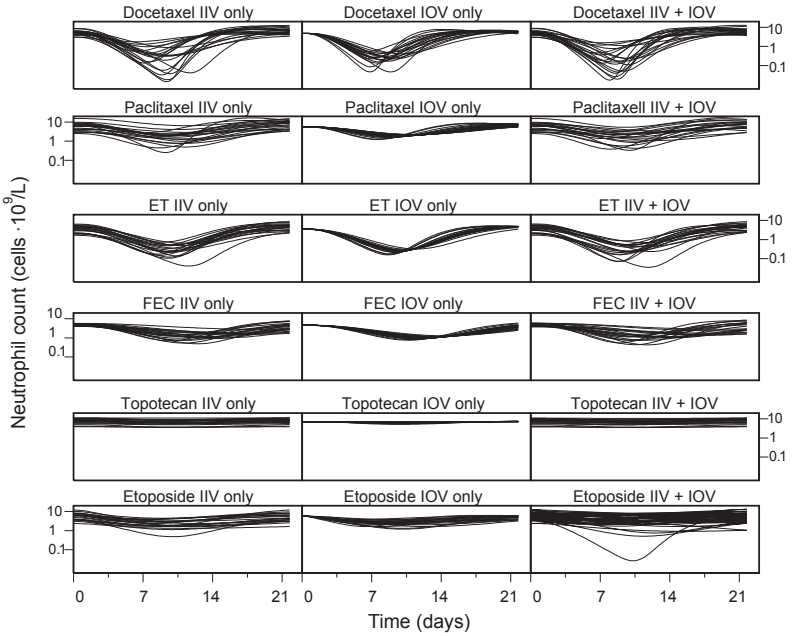

Fig. 4 Twenty simulated individual time-courses of myelosuppression including IIV only, IOV only or IIV and IOV for all the six investigated datasets

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 x 10^9/L.

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

For none of the data sets 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.

IOV 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* [29]. 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.

PK were 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 [12, 13, 29]. The estimated IOV in clearance ranged between 14-18 %.

Two alternative a posteriori dosing strategies to traditional dose adjustments in predefined steps are pharmacokinetic and pharmacodynamic adaptive control [30]. The adaptive control strategies have been successfully evaluated in the clinic for some antineoplastic agents [31, 32]. 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 [31, 32]. 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 data sets 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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