Cancer Chemother Pharmacol (2012) 69:881–890
DOI 10.1007/s00280-011-1769-7

ORIGINAL ARTICLE

The shape of the myelosuppression time profile is related to the probability of developing neutropenic fever in patients with docetaxel-induced grade IV neutropenia

Emma K. Hansson · Lena E. Friberg

Received: 19 August 2011 / Accepted: 14 October 2011 / Published online: 5 November 2011

Abstract
Purpose Chemotherapy-induced neutropenia is associated with the risk of developing febrile neutropenia (FN). The aim was to describe the time course of myelosuppression in breast cancer patients treated with docetaxel and to investigate how the shape of the predicted myelosuppression time course and earlier proposed risk factors influence the probability of developing FN.
Methods Neutrophil counts from 140 breast cancer patients with observed grade IV neutropenia during the first course of docetaxel treatment were included. Twenty-six of the patients (19%) experienced FN. The myelosuppression time course was described using a semi-mechanistic myelosuppression model in NONMEM. The individual myelosuppression model parameters [baseline neutrophil count, mean transit time (MTT) and drug effect parameter (EC_{50})], myelosuppression descriptors (nadir, duration of grade IV neutropenia) and earlier suggested risk factors (age, performance status, haemoglobin and liver function) were explored to be related to FN by logistic regression.
Results The neutrophil time course following docetaxel treatment was well described by the model. EC_{50} and MTT were both significantly related to the probability of developing FN where low parameter values result in a rapid decline, low nadir and an increased risk of FN. None of the evaluated risk factors or myelosuppression descriptors were significant.
Conclusion The probability to develop FN in patients who experience grade IV neutropenia was dependent on the myelosuppression time profile. Patients with a rapid neutrophil decline and high drug sensitivity had a higher probability to develop FN. Model-based parameter estimates were superior predictors over descriptive values such as the nadir or duration of neutropenia.

Keywords Oncology · Haematological toxicity · Febrile neutropenia · NONMEM

Introduction

Chemotherapy-induced neutropenia is the most common and often dose limiting toxicity of cytotoxic anticancer treatment [1]. Neutropenia, i.e., an absolute neutrophil count (ANC) of $<1.5 \times 10^9$/L [2], increases the patients' susceptibility to the development of infections. Four different grades are related to the severity of neutropenia where grade IV neutropenia (ANC $< 0.5 \times 10^9$/L) is considered life-threatening or disabling [2]. Neutropenia may result in the development of febrile neutropenia (FN) which is known to be associated with important morbidity, mortality and treatment costs [3]. FN was here defined, according to the definition used by, e.g., Infectious Disease Society America (IDSA) and European Organization for Research and Treatment of Cancer (EORTC), as observed grade IV neutropenia in combination with fever (oral temperature >38.5°C) [4, 5].

Grade IV neutropenia and FN often result in treatment discontinuation, dose reductions and/or delays which ultimately may compromise the long-term clinical outcome [1]. A correlation between reduced dose intensity and a worse prognosis with respect to disease-free and overall survival has however been observed in, e.g., breast cancer patients [6, 7]. A reduced dose is of particular concern when treatment is given with a curative intent such as in

E. K. Hansson (✉) · L. E. Friberg
Department of Pharmaceutical Biosciences,
Uppsala University, Box 591, 751 24 Uppsala, Sweden
e-mail: emma.hansson@farmbio.uu.se

the adjuvant setting. Also, an association between a higher grade of myelosuppression and improved overall survival has been established [8–11]. A better understanding of the causes of FN to identify patients at risk, without jeopardizing the treatment effect by, e.g., unnecessary dose reductions, would therefore be valuable.

The risk of developing FN is reduced by the administration of prophylactic granulocyte-stimulating factors (G-CSF) and antibiotics [12–14]. The routine use of prophylactic treatment is however questioned due to the high expenses of G-CSF treatment and the emergence of antibiotic resistance. Guidelines are available to help identifying patients most likely to benefit from the prophylactic treatment [4, 5, 15]. Identified risk factors that predispose patients to increased complications from prolonged neutropenia are cancer type, type of chemotherapy treatment and patient-specific risk factors such as age (>65 years), female gender, advanced disease, previous episodes of FN, poor performance status, haemoglobin <12 g/dL, and liver, renal or cardiovascular disease [5, 15].

Even though several risk factors for an increased probability of complications from neutropenia have been suggested and several risk models have been proposed, see e.g. [16, 17], FN remains a common life-threatening adverse event of cancer chemotherapy. A gain in the understanding why some patients develop FN is important to enhance the efficacy of cytotoxic chemotherapy treatment, the use of health care resources and the patient's physical well-being.

It was early recognized that complications of neutropenia are related to both the extent and duration of neutropenia. [18]. It is then of importance to consider not only the extent of neutropenia, e.g., observed nadir, but also the entire time course of myelosuppression when learning more about FN. Usually measurements of blood cell counts are only made once, or at a few predetermined time points during a treatment cycle and therefore do not give an accurate description of the real time-course of neutropenia in a patient. By the use of population pharmacokinetic–pharmacodynamic (PKPD) modelling, the relationship between plasma drug concentrations and the myelosuppression time course can be predicted and gives insight into what role the myelosuppression profile plays in the development of FN. Also, patient-specific risk factors can be identified. As grade IV neutropenia is a constraint to be diagnosed with FN, an investigation of risk factors for FN would need to focus on a population of grade IV neutropenia patients.

A semi-mechanistic model describing the full-time course of chemotherapy-induced myelosuppression has been developed (Fig. 1) [19] and applied to several different anticancer drugs showing consistency in the system-related parameters [20–26]. The model mimics the myelopoiesis and consists of a compartment representing proliferative cells in the bone marrow, three maturation compartments with drug-insensitive cells and one compartment reflecting circulating neutrophils in the blood. A feedback mechanism, regulating the proliferative rate when the numbers of circulating neutrophils are low, is also included. Estimated parameters are the system-related parameters, baseline neutrophil count (ANC_0), mean transit time (MTT) and feedback factor (γ) as well as the drug effect parameters (Slope for a linear model or E_{max} and EC_{50} for an E_{max} model). The model provides a good characterization of the full time course of myelosuppression and can thereby form the basis when exploring how neutropenia is related to FN.

The aim of the present study was to describe the time course of myelosuppression in breast cancer patients treated with docetaxel and to investigate how the shape of the predicted myelosuppression time course and earlier proposed patient-specific risk factors (age, performance status, haemoglobin level and liver function) influence the probability of developing FN in patients with grade IV neutropenia.

Methods

Patients and treatment

Neutrophil counts ($n = 2{,}262$) and information about febrile neutropenic (FN) episodes in 244 patients with locally advanced and/or metastatic breast cancer treated with single-agent docetaxel were available [27]. The patients were part of the active control group in a phase III trial studying the combination treatment of capecitabine and docetaxel. Patients known to have received granulocyte colony-stimulating factor (G-CSF) were excluded from the data analysis. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committees.

The initial dose level of docetaxel was 100 or 75 mg/m^2 (if mild hepatic impairment, $n = 10$) infused intravenously over 1 h every 3 weeks. Neutrophil measurements were according to the nominal sampling scheme sampled prior to treatment, at days 8 and 21 in the first treatment cycle and at day 21 in the subsequent cycles. On the occurrence of grade IV neutropenia, additional blood samples were taken.

Since FN here was defined as fever in combination with grade IV neutropenia, only patients who developed grade IV neutropenia ($n = 140$, 57%) during the first treatment course were included in the development of the FN model. By only including individuals with grade IV neutropenia, risk factors for FN occurrence will be distinguished from grade IV risk factors. The neutrophil data for all patients were also characterized for comparison purposes.

The occurrence of grade IV neutropenia was identified based on the observed neutrophil counts ($n = 820$) in the first treatment cycle. Only data from treatment cycle 1 were included as limited neutrophil data were available from

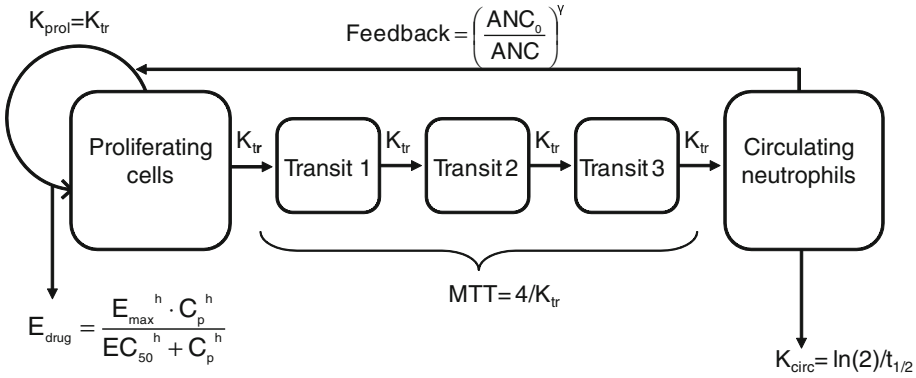

Fig. 1 The semi-mechanistic model of myelosuppression with the estimated structural model parameters (ANC_0), mean transit time (MTT), feedback factor γ and the drug effect parameters (E_{max} and EC_{50}). K_{tr}, transit rate constant; K_{circ}, elimination rate constant for circulating neutrophils; and $(ANC_0/ANC)^{\gamma}$, feedback loop from the circulating neutrophils regulating the proliferative rate

cycle 2 and onwards, limiting the possibility to classify whether the patients developed grade IV neutropenia. In addition, most events of FN (55%) occurred in the first treatment cycle with relatively few episodes of FN in subsequent cycles.

Data on the earlier proposed patient-specific risk factors [5, 15] (age, performance status, haemoglobin level and liver function) were available. A data summary of the analysed risk factors is presented in Table 1. Twenty-six events of FN (19%) occurred in the 140 patients with observed grade IV neutropenia during the first treatment cycle. Information about the date of onset of FN, dose adjustments and outcome was available for the patients developing FN. The median (range) time to the identification of FN was 7 (6–9) days after treatment, and the duration of FN was 7 (3–11) days.

Table 1 Data summary for evaluated risk factors (baseline observations) in individuals with observed grade IV neutropenia

Risk factor	Median	Range
Age (years)	52.5	28–75
Haemoglobin (μmol/L)	7.69	5.39–9.4
ALP (×ULN)	2.11	0.63–20.7
ASAT (×ULN)	0.48	0.02–3.00
ALAT (×ULN)	0.42	0.07–2.97
Bilirubin, total (mmol/L)	144.5	17.1–497.6
		%
Karnofsky performance score of 70		14.3
Karnofsky performance score of 80		26.4
Karnofsky performance score of 90		32.9
Karnofsky performance score of 100		24.3

Data analysis

The non-linear mixed-effects modelling approach using NONMEM VI and 7 [28] was applied to describe the myelosuppression time course and to identify potential differences between patients developing FN compared to other patients experiencing grade IV neutropenia. The PsN toolkit (version 3) was used for post-processing of results [29, 30] and the R-based software Xpose (version 4) [31] for creating graphical diagnostics.

Model selection was guided by graphical assessment of goodness of fit plots and the change in the objective function value (OFV) computed by NONMEM in the likelihood ratio test. For two nested models, the change in OFV is equal to minus twice the log likelihood and approximately χ^2 distributed. A significance level of $P < 0.01$ was used corresponding to a difference in OFV of >-6.63 for the addition of one parameter.

Myelosuppression model

The pharmacokinetics of docetaxel was described by concentration–time profiles predicted using typical population PK parameters from a previously developed PK model [32] as no individual PK data were available. The myelosuppression time courses following up to 16 cycles of docetaxel treatment in the studied population have been characterized previously in order to investigate the magnitude of inter-occasion variability in myelosuppression model parameters [25]. Here, the first treatment cycle was described for (scenario a) all patients and (scenario b) for only individuals who developed grade IV neutropenia using a semi-mechanistic model for chemotherapy-induced myelosuppression (Fig. 1) [19].

The myelosuppression model was fitted to neutrophil data using the Laplacian estimation method in NONMEM. 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 [33, 34]. The half-life of circulating neutrophils in blood was here fixed to the literature value of 7 h [35] as we believe it is more mechanistic instead of forcing the half-life to be dependent on the MTT estimate as in the original model [19]. In the

semi-mechanistic myelosuppression model, the drug is assumed to act by reducing the proliferation rate and inducing cell loss. In the original publication, the drug effect was modelled as being a linear function or an E_{max} function of the drug concentration [19]. Here, a sigmoidal E_{max} model was in addition evaluated for improvement in the model fit. Interindividual variability (IIV) was assumed to be log-normally distributed with a mean of zero and variances ω^2 and was evaluated for ANC_0, MTT, γ and Slope (or EC_{50} and E_{max} for the E_{max} model). An additive (on Box-Cox scale) residual error model was used to describe the random residual variability.

Precision in myelosuppression model parameter estimates was determined using a non-parametric bootstrap procedure with 100 samples generated for the calculation of standard errors of the parameters. The predictive performance of the myelosuppression model was judged based on the assessment of a visual predictive check (VPC) [36]. The median and the 5th and 95th percentiles of the prediction intervals were derived from 500 simulated replicates of the data set 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 5th and 95th percentiles, the 95% confidence intervals were calculated from the simulated data sets.

Probability of FN

Following the description of the myelosuppression time courses, a sequential fit (PPP&D) [37] of the neutrophil data in the individuals with observed grade IV neutropenia (scenario b) and the probability of developing FN was performed. The sequential approach (PPP&D) was chosen for demonstrated good performance [37], practical reasons and to avoid that the logistic regression model was driving the description of the myelosuppression time course if fitted simultaneously. A dichotomous scale was used for the FN data where 1 represented an episode of FN and 0 no episode of FN. The variables that were explored to be related to the probability of FN data by a logistic regression model were; all myelosuppression model parameters where interindividual variability was of significance, predicted myelosuppression descriptors (nadir and duration of grade IV neutropenia) and proposed risk factors [5, 15] (age >65 years, performance status, haemoglobin level <12 g/dL and liver function).

Given the assumption that P is the probability of developing FN, the model had the following general structure (Eqs. 1, 2):

$$\text{Logit}(P) = \ln\left(\frac{P}{1-P}\right) = \theta_1 + f(\text{myelosuppresion}) + f(\text{risk factors}) \quad (1)$$

$$P = \frac{\exp(\theta_1 + f(\text{myelosuppresion}) + f(\text{risk factor}))}{1 + \exp(\theta_1 + f(\text{myelosuppresion}) + f(\text{risk factor})} \quad (2)$$

where θ_1 is the intercept, f(myelosuppression) the probability function for developing FN given myelosuppression model parameters and descriptors, and f(risk factors) the function relating the investigated risk factors with the probability of developing FN. For f(myelosuppression) linear, E_{max}, sigmoidal E_{max} and power functions were evaluated. The proposed risk factors were evaluated for statistical significance ($P < 0.05$ forward inclusion and $P < 0.01$ for backward exclusion) using the automated stepwise covariate model building method (SCM) in PsN. Linear, and if linear models were significant, non-linear relationships were evaluated.

Reliability in the parameters describing the relationship with FN was determined using a non-parametric bootstrap procedure with 100 samples. The FN model appropriateness was assessed by applying a categorical visual predictive check [38] and by comparing number of simulated events and observed. The categorical visual predictive check was created by simulating 500 data sets. The observed and the simulated fraction of observations were plotted against the independent variable and were compared with a 95% confidence interval based on the simulations. Also, 500 data sets were simulated using parameter estimates from the semi-mechanistic myelosuppression model including all individuals (scenario a) and the logistic regression parameter estimates from the final FN model. The probability of FN occurrence (yes/no) was determined in individuals who were simulated to develop grade IV neutropenia. The number of events of grade IV neutropenia and FN was calculated in each simulated data set and compared with the number of observed events in the original data set.

Results

Myelosuppression model

The myelosuppression model could well characterize the neutrophil time course following docetaxel treatment (scenario a) in all patients and (scenario b) in the patients who experienced grade IV neutropenia. A sigmoidal E_{max} function described the data significantly better than a basic E_{max} model or a linear drug–effect relationship and improved the prediction of the time course around nadir.

The earlier description of the haematological toxicity in the investigated population included a linear drug–effect relationship [25]. The system-related parameter estimates for ANC_0 and γ were in accordance with the previously estimated parameters for other anticancer drug treatments and as previously observed was MTT relatively short for docetaxel-treated patients [19, 25] (Table 2). Here, IIV was also included for gamma. The myelosuppression model parameter estimates were as expected somewhat different when only individuals with grade IV neutropenia (scenario b) in the first treatment course were included in the myelosuppression characterization compared to when all data were used. For example, the parameter MTT was shorter, EC_{50} was lower and E_{max} was higher when only patients with grade IV neutropenia were analysed. The predictive performance of the semi-mechanistic myelosuppression model, as illustrated by visual predictive checks, was reasonable both when evaluating the model for (scenario a) all patients and when (scenario b) only grade IV patients were included (Fig. 2). The lower neutrophil counts, which here are the most important part of the neutrophil time course to characterize, were especially well characterized. Also, the simulated median number of individuals ($n = 136$) with grade IV neutropenia was well in accordance with the observed number ($n = 140$) (Fig. 3).

Probability of FN

The myelosuppression model parameters describing the drug potency (EC_{50}) ($\Delta OFV = 48$) and the time through the chain of non-mitotic bone marrow cell compartments (MTT) ($\Delta OFV = 39$) were both significantly related to the probability of developing FN with a power function including the constant parameters c and d. The individual value was normalized to the predicted median of the population (TVEC50 and TVMTT) (Table 2) (Eqs. 3–5). Individuals with a short predicted MTT and a low EC_{50} value have an early and low nadir and an increased risk of developing FN. The impact of MTT and EC_{50} on the predicted myelosuppression profile is illustrated in Fig. 4. The probability of FN increased from 0% for the patients with highest estimated EC_{50} and MTT values to 42% for patients with the lowest values. Allowing for an interaction between MTT and EC_{50} did not increase the predictability of FN. None of the other evaluated risk factors or myelosuppression descriptors was significant when EC_{50} and MTT had been included in the model.

$$f(\mathrm{EC}_{50}) = c_{\mathrm{EC}_{50}} \left(\frac{\mathrm{EC}_{50}}{\mathrm{TVEC}_{50}} \right)^{d_{\mathrm{EC}_{50}}} \quad (3)$$

$$f(\mathrm{MTT}) = c_{\mathrm{MTT}} \left(\frac{\mathrm{MTT}}{\mathrm{TVMTT}} \right)^{d_{\mathrm{MTT}}} \quad (4)$$

$$P = \frac{\exp(\theta_1 + f(\mathrm{MTT}) + f(\mathrm{EC}_{50}))}{1 + \exp(\theta_1 + f(\mathrm{MTT}) + f(\mathrm{EC}_{50}))} \quad (5)$$

The parameters in the logistic regression model were estimated with high precision (Table 2). The myelosuppression and logistic regression models were found adequate for simulations as the observed number of individuals with grade IV neutropenia and observed numbers of FN events were within the 90th prediction intervals of the simulated number of events (Fig. 3). Also,

Table 2 Final population model parameter estimates and relative SE % (calculated from bootstrap results) of the docetaxel semi-mechanistic myelosuppression model and for the logistic regression model for the probability of FN occurrence

Parameter	(a) All individuals				(b) Individuals with grade IV			
	Estimate	RSE (%)	IIV (CV %)	RSE (%)	Estimate	RSE (%)	IIV (CV %)	RSE (%)
ANC_0 ($\times 10^9$/L)	4.65	3.4	32	8.6	4.65	1.7	32	5.3
MTT (h)	86.5	3.6	19	9.2	78.3	2.1	12	5.5
γ	0.159	3.7	20	12	0.155	3.2	24	8.1
E_{max}	91.3	6.6	–	–	95.1	4.9	–	–
EC_{50} (mg/L)	1.50	8.4	68	7.4	1.39	10	36	9.4
h	1.64	9.9	–	–	1.45	10	–	–
Residual error[a]	0.497	5.5	–	–	0.468	5.1		–
FN model								
θ_1					−0.360	32		
c_{EC50}					−0.160	21		
d_{EC50}					7.76	11		
c_{MTT}					−0.122	43		
d_{MTT}					25.4	8.3		

IIV inter individual variability, *RSE* relative standard error

[a] Additive error on Box-Cox scale

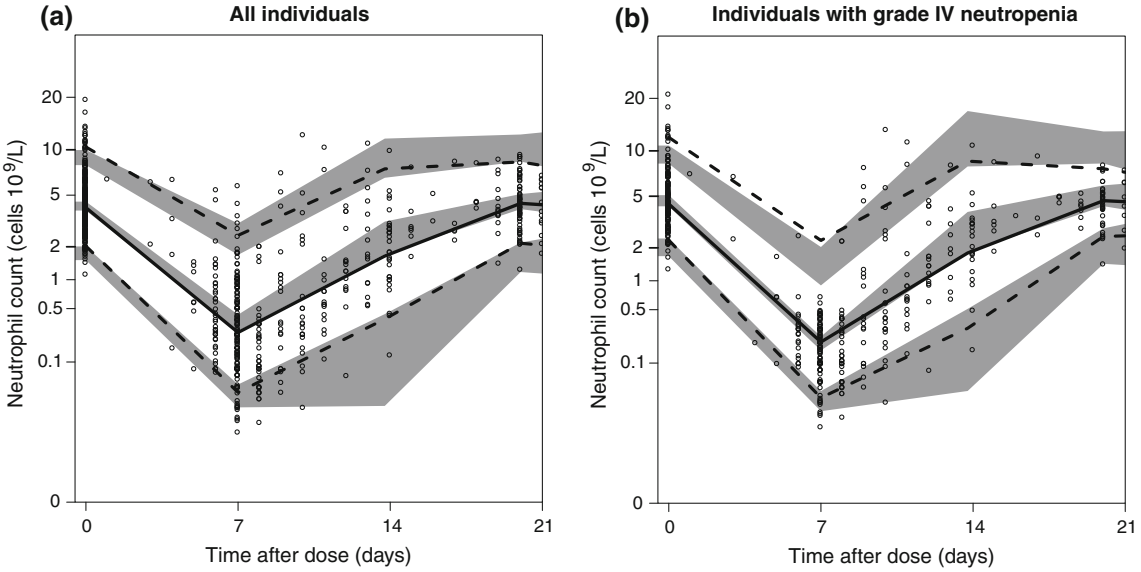

Fig. 2 VPCs of the final semi-mechanistic myelosuppression models for (scenario **a**) all patients (*left*) and (scenario **b**) only patients with observed grade IV neutropenia (*right*). The circles represent observed data, the *solid line* the median of the observed data and the *dashed lines* the 5th and 95th percentiles of the observed data. *Shaded* areas are the confidence intervals based on the simulated data's 5th, 50th and 95th percentiles

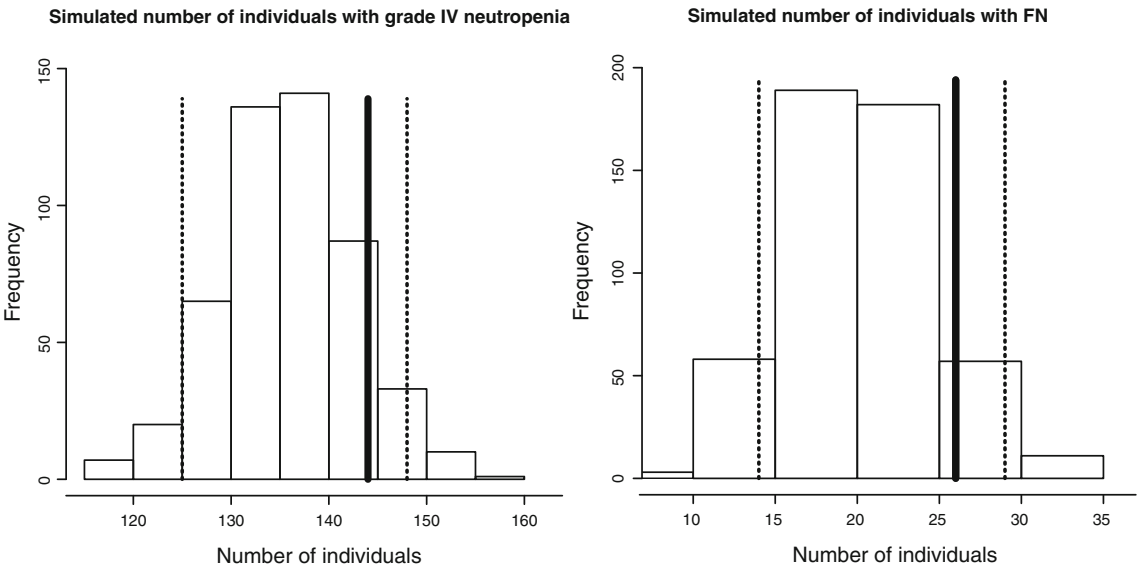

Fig. 3 Assessment of the appropriateness of the FN model by simulations of 500 data sets. Histograms represent the number of simulated individuals with grade IV neutropenia (*left*) and FN events (*right*). The *solid lines* represent the observed number of events in the analysed data set, and the *dashed lines* represent the 5th and 95th percentiles of the simulated number of events

the categorical VPC (Fig. 5) shows that the proportion of observed data stratified by predicted MTT and EC_{50} was within the 95% confidence interval.

Discussion

FN is a serious complication of myelosuppressive chemotherapy and is associated with significant morbidity, mortality and high treatment costs [3]. By the use of the semi-mechanistic myelosuppression model [19], the entire individual time-course of the changes in blood cell count, despite sparse data, could be taken into account in defining the relationship with the probability of FN. A logistic regression model was developed in NONMEM with the predicted myelosuppression time profile as a predictor for the probability of developing FN. The drug effect parameter EC_{50} and the mean transit time through the non-mitotic

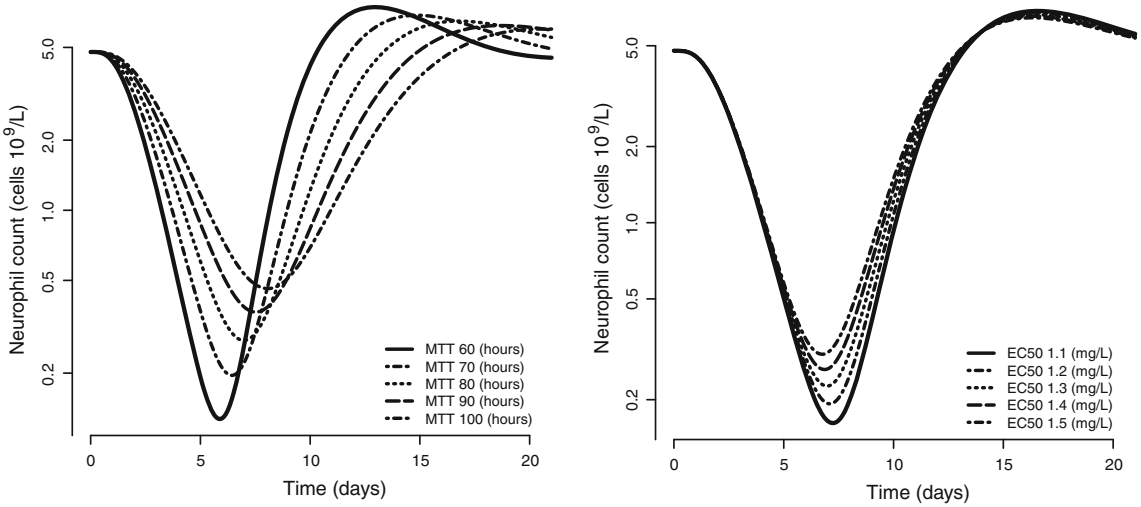

Fig. 4 An illustration of how the myelosuppression model parameters MTT (*left*) and EC_{50}'s (*right*) impact on the predicted myelosuppression time profile. MTT was varied between 60 and 100 h, and EC_{50} between 1.1 and 1.5 mg/L

maturation chain, MTT, were found significant, which indicates that patients with high drug sensitivity and a fast decline in neutrophils are more likely to develop FN, i.e., a combination of several factors such as onset, duration and grade of neutropenia are important. Predicted or observed baseline neutrophil count was not significantly related to the probability of developing FN in this group of patients that included only those who experienced grade IV neutropenia.

The predictive performance of the FN model was sufficient although the simulated median number of events was slightly lower ($n = 21$) than the observed number of events ($n = 26$) (Fig. 4). An important risk factor that could not be considered here and that might improve the predictability further is the degree of tissue damage caused by the cytotoxic agents in the gastrointestinal tract which allows infections to develop [18].

Bruno et al. [39] and Ozawa et al. [40] have previously reported on logistic regression models for covariates associated with the occurrence on FN in docetaxel-treated cancer patients. A high clearance and an increased AAG (α-1-acid glycoprotein) level indicated a lower risk of FN in the model proposed by Bruno et al., and a worse performance status and a higher drug exposure (AUC) were predictors of FN in the Ozawa et al. model. None of the evaluated earlier proposed patient-specific risk factors for FN occurrence [5, 15] were here found significant when MTT and EC_{50} were included in the model. It is however unclear whether the earlier proposed risk factors [5, 15] and identified predictors [39, 40] for FN are solely risk factors for FN occurrence or whether they are also risk factors for developing grade IV neutropenia, as earlier analyses have been based on the total study population and not only on individuals with grade IV neutropenia. Here, we have made

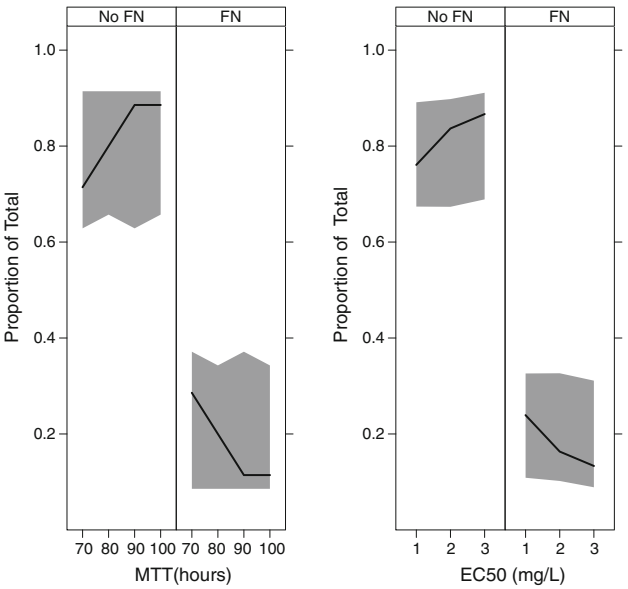

Fig. 5 Categorical visual predictive check stratified by predicted MTT and EC_{50}. The solid line represents the proportion of predicted MTT and EC_{50} values, and the shaded area is the 95% confidence interval based on simulations

an attempt to distinguish risk factors for FN occurrence from risk factors of grade IV neutropenia by only including individuals with grade IV. This analysis included a fairly large amount of neutrophil data, and relatively many of the patients experiencing grade IV neutropenia developed FN.

Bodey et al. [18] early found the relationship between the degree and duration of neutropenia and the risk of developing infections in patients with leukaemia. The current analysis shows that the probability of FN in patients treated with docetaxel is not only dependent on the duration and extent of neutropenia but also the rate, i.e., the

whole shape of the myelosuppression time course is important. Patients developing FN were predicted to have an earlier and lower nadir than patients who have a small risk. This is also in line with that docetaxel has an early (median time to nadir 7 days) and low nadir value [41] at therapeutic dose levels and is associated with a relatively high incidence of FN compared with other cytotoxic anticancer drugs [5, 15]. A continuation of this work would be to investigate whether the same relationship between the shape of the myelosuppression time profile and FN can be identified with other cytotoxic anticancer treatments in other patient populations.

Also, explaining why some patients have a more rapid and pronounced decline in neutrophil counts and thereby be able to a priori identify patients at high risk is important since most episodes of FN occur in the first treatment cycle [42, 43]. Factors predictive of the drug-specific parameter EC_{50} and the system-specific parameter MTT would be of value. Kloft et al. [26] identified age as being influential (minor) on MTT with older patients having a shorter MTT. Age was not here found to be a significant risk factor, but it is noteworthy that only a small proportion of the patients were >65 years (15%). Baseline AAG level (α-1-acid glycoprotein) has in analyses where AAG was included as a covariate for PK also been identified as a significant covariate for the drug specific model parameter (Slope) following docetaxel treatment [26, 44]. Puisset et al. [44] , however, judged AAG to have a minor impact on Slope due to its simultaneous effect on CL.

Another attractive possibility to early identify patients at risk for FN would be to measure the neutrophil count at the start of treatment and before the expected nadir, e.g. at treatment day 4 or 5, and, together with support of the model and its population parameters, estimate the risk of FN and need for initiation of prophylactic treatment. Wallin et al. [45] showed that a baseline and a near nadir sample was sufficient to accurately predict the individual parameter estimates of the myelosuppression model. The results indicate that only limited information on neutrophils is needed for Bayesian estimation of individual model parameters. However, further prospective studies are needed to evaluate the clinical utility of such an approach.

It would also be useful to be able to identify patients with a high probability of developing FN based on the information on myelosuppression from previous treatment courses and thereby avoid unnecessary dose reductions. The information could thereby be incorporated in the determination of the maximal acceptable dose level for an individual patient, e.g., by incorporating the information in a recently developed model-based tool for dose individualization based on neutrophil counts [46].

Because of the limited information on neutropenia in subsequent courses, the current analysis only focused on the first treatment course. Why episodes of FN were observed to be less common in subsequent treatment cycles is therefore hard to conclude, but it may at least partly be due to the fact that patients experiencing severe neutropenia received a lower dose in subsequent treatment cycles to avoid more neutropenic episodes or due to the dropout of vulnerable patients from the study because of disease progression.

In conclusion, the probability to develop FN in patients who experience grade IV neutropenia is dependent on the myelosuppression time profile as here illustrated following docetaxel treatment. Patients with a rapid neutrophil decline and high drug sensitivity have a higher probability to develop FN compared with other patients who experience grade IV neutropenia. Model-based parameter estimates were superior predictors over descriptive values such as the nadir or duration of neutropenia.

Acknowledgments The authors would like to thank F. Hoffman La-Roche Ltd. for kindly providing the data and Franziska Schaedeli Stark for valuable comments during the preparation of the manuscript. The study was financially supported by the Swedish Cancer Society.

Conflict of interest None.

References

1. Crawford J, Dale DC, Lyman GH (2004) Chemotherapy-induced neutropenia—risks, consequences, and new directions for its management. Cancer 100(2):228–237
2. National Cancer Institute, National (2006) Common terminology criteria for adverse events v3.0. Available at http://www.eortc.be/services/doc/ctc/ctcaev3.pdf
3. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH (2006) Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 106(10):2258–2266
4. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JAH, Wingard JR (2011) Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 52(4):427–431
5. Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JP, Kearney N, Lyman GH, Pettengell R, Tjan-Heijnen VC, Walewski J, Weber DC, Zielinski C (2011) 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer 47(1):8–32
6. Bonadonna G, Moliterni A, Zambetti M, Daidone MG, Pilotti S, Gianni L, Valagussa P (2005) 30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: cohort study. Br Med J 330(7485):217–220
7. Budman DR, Berry DA, Cirrincione CT, Henderson IC, Wood WC, Weiss RB, Ferree CR, Muss HB, Green MR, Norton L, Frei E (1998) Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. J Natl Cancer Inst 90(16):1205–1211
8. Mayers C, Panzarella T, Tannock IF (2001) Analysis of the prognostic effects of inclusion in a clinical trial and of myelosuppression on survival after adjuvant chemotherapy for breast carcinoma. Cancer 91(12):2246–2257

9. Poikonen P, Saarto T, Lundin J, Joensuu H, Blomqvist C (1999) Leucocyte nadir as a marker for chemotherapy efficacy in node-positive breast cancer treated with adjuvant CMF. Br J Cancer 80(11):1763–1766
10. Cameron DA, Massie C, Kerr G, Leonard RCF (2003) Moderate neutropenia with adjuvant CMF confers improved survival in early breast cancer. Br J Cancer 89(10):1837–1842
11. Saarto T, Blomqvist C, Rissanen P, Auvinen A, Elomaa I (1997) Haematological toxicity: a marker of adjuvant chemotherapy efficacy in stage II and III breast cancer. Br J Cancer 75(2): 301–305
12. Pascoe J, Cullen M (2006) The prevention of febrile neutropenia. Curr Opin Oncol 18(4):325–329
13. Timmer-Bonte JNH, Tjan-Heijnen VCG (2006) Febrile neutropenia: highlighting the role of prophylactic antibiotics and granulocyte colony-stimulating factor during standard dose chemotherapy for solid tumors. Anticancer Drugs 17(8):881–889
14. Wingard JR, Elmongy M (2009) Strategies for minimizing complications of neutropenia: prophylactic myeloid growth factors or antibiotics. Crit Rev Oncol Hematol 72(2):144–154
15. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Bennett CL, Cantor SB, Crawford J, Cross SJ, Demetri G, Desch CE, Pizzo PA, Schiffer CA, Schwartzberg L, Somerfield MR, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ, Wolff AC (2006) 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 24(19):3187–3205
16. Lyman GH, Lyman CH, Agboola O (2005) Risk models for predicting chemotherapy-induced neutropenia. Oncologist 10(6):427–437
17. Lyman GH, Kuderer NM, Crawford J, Wolff DA, Culakova E, Poniewierski MS, Dale DC (2011) Predicting individual risk of neutropenic complications in patients receiving cancer chemotherapy. Cancer 117(9):1917–1927. doi:10.1002/cncr.25691
18. Bodey GP, Buckley M, Sathe YS, Freireic EJ (1966) Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 64(2):328–340
19. Friberg LE, Henningsson A, Maas H, Nguyen L, Karlsson MO (2002) Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. J Clin Oncol 20(24): 4713–4721
20. Sandstrom M, Lindman H, Nygren P, Lidbrink E, Bergh J, Karlsson MO (2005) Model describing the relationship between pharmacokinetics and hematologic toxicity of the epirubicin-docetaxel regimen in breast cancer patients. J Clin Oncol 23(3):413–421
21. Sandstrom M, Lindman H, Nygren P, Johansson M, Bergh J, Karlsson MO (2006) Population analysis of the pharmacokinetics and the haematological toxicity of the fluorouracil-epirubicin-cyclophosphamide regimen in breast cancer patients. Cancer Chemother Pharmacol 58(2):143–156
22. Troconiz IF, Garrido MJ, Segura C, Cendros JM, Principe P, Peraire C, Obach R (2006) Phase I dose-finding study and a pharmacokinetic/pharmacodynamic analysis of the neutropenic response of intravenous diflomotecan in patients with advanced malignant tumours. Cancer Chemother Pharmacol 57(6):727–735
23. Leger F, Loos WJ, Bugat R, Mathijssen RH, Goffinet M, Verweij J, Sparreboom A, Chatelut E (2004) Mechanism-based models for topotecan-induced neutropenia. Clin Pharmacol Ther 76(6): 567–578
24. Latz J, Karlsson MO, Rusthoven JJ, Ghosh A, Johnson RD (2006) A semimechanistic-physiologic population pharmacokinetic/pharmacodynamic model for neutropenia following pemetrexed therapy. Cancer Chemother Pharmacol 57(4):412–426
25. Hansson EK, Wallin JE, Lindman H, Sandstrom M, Karlsson MO, Friberg LE (2010) Limited inter-occasion variability in relation to inter-individual variability in chemotherapy-induced myelosuppression. Cancer Chemother Pharmacol 65(5):839–848
26. Kloft C, Wallin J, Henningsson A, Chatelut E, Karlsson MO (2006) Population pharmacokinetic-pharmacodynamic model for neutropenia with patient subgroup identification: comparison across anticancer drugs. Clin Cancer Res 12(18):5481–5490
27. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, Fumoleau P, Jones S, Lui WY, Mauriac L, Twelves C, Van Hazel G, Verma S, Leonard R (2002) Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 20(12):2812–2823
28. Beal S, Sheiner L, Boekmann A, Bauer RJ (2009) NONMEM user's guides (1989–2006). Icon Development Solutions, Ellicott City
29. Lindbom L, Ribbing J, Jonsson EN (2004) Perls-speaks-NONMEM (PsN)—a Perl module for NONMEM related programming. Comput Methods Programs Biomed 75(2):85–94
30. Lindbom L, Pihlgren P, Jonsson EN (2005) PsN-toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed 80(3):241–257
31. Jonsson EN, Karlsson MO (1999) Xpose:an Splus based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. Comput Methods Programs Biomed 58:51–64
32. Bruno R, Vivier N, Vergniol JC, DePhillips SL, Montay G, Sheiner LB (1996) A population pharmacokinetic model for docetaxel (Taxotere(R)): model building and validation. J Pharmacokinet Biopharm 24(2):153–172
33. Karlsson MO, Port RE, Ratain MJ, Sheiner LB (1995) A population-model for the leukopenic effect of etoposide. Clin Pharmacol Ther 55(2):325–335
34. Friberg LE, Brindley CJ, Karlsson MO, Devlin AJ (2000) Models of schedule dependent haematological toxicity of 2'-deoxy-2'-methylidenecytidine (DMDC). Eur J Clin Pharmacol 56(8): 567–574
35. Cartwright GE, Athens JW, Wintrobe MM (1964) The kinetics of granulopoiesis in normal man. Blood 24(6):780–803
36. Karlsson MO, Holford NHG (2008) A tutorial on visual predictive checks, p 17, Abstr 1434. http://wwwpage-meetingorg/?abstract=1434
37. Zhang L, Beal SL, Sheiner LB (2003) Simultaneous vs. sequential analysis for population PK/PD data I: best-case performance. J Pharmacokinet Pharmacodyn 30(6):387–404
38. Bergstrand M, Hooker AC, Karlsson MO (2009) Visual predictive checks for censored and categorical data, p 18, Abstr 1604. http://wwwpage-meetingorg/?abstract=1604
39. Bruno R, Hille D, Riva A, Vivier N, Huinnink W, van Oosterom AT, Kaye SB, Verweij J, Fossella FV, Valero V, Rigas JR, Seidman AD, Chevallier B, Fumoleau P, Burris HA, Ravclin PM, Sheiner LB (1998) Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. J Clin Oncol 16(1):187–196
40. Ozawa K, Minami H, Sato H (2008) Logistic regression analysis for febrile neutropenia (FN) induced by docetaxel in Japanese cancer patients. Cancer Chemother Pharmacol 62(3):551–557
41. Valero V (1997) Docetaxel as single-agent therapy in metastatic breast cancer: clinical efficacy. Semin Oncol 24(4):S11–S18
42. Lyman GH, Delgado DJ (2003) Risk and timing of hospitalization for febrile neutropenia in patients receiving CHOP, CHOP-R, or CNOP chemotherapy for intermediate-grade non-Hodgkin lymphoma. Cancer 98(11):2402–2409
43. Crawford J, Dale DC, Kuderer NM, Culakova E, Poniewierski MS, Wolff D, Lyman GH (2008) Risk and timing of neutropenic events in adult cancer patients receiving chemotherapy: the results of a prospective nationwide study of oncology practice. J Natl Compr Canc Netw 6(2):109–118

44. Puisset F, Alexandre J, Treluyer JM, Raoul V, Roche H, Goldwasser F, Chatelut E (2007) Clinical pharmacodynamic factors in docetaxel toxicity. Br J Cancer 97(3):290–296
45. Wallin J, Friberg LE, Karlsson MO (2010) Model-based neutrophil guided dose adaptation in chemotherapy: evaluation of predicted outcome with different types and amounts of information. Basic Clin Pharmacol Toxicol 106(3):234–242
46. Wallin J, Friberg LE, Karlsson MO (2009) A tool for neutrophil guided dose adaptation in chemotherapy. Comput Methods Programs Biomed 93(13):283–291