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ORIGINAL ARTICLE

Mechanism-based pharmacokinetic/pharmacodynamic model for troxacitabine-induced neutropenia in cancer patients

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Abstract
Purposes The objective of this study was to develop a mechanism-based population pharmacokinetic/pharmacodynamic (PK/PD) model in describing troxacitabine-induced neutropenia in patients with cancer.
Methods A total of 727 PK/PD samples from 31 patients with cancer were included in the analysis. A mechanism-based population PD model was developed to describe neutropenia and the final model consisted of (1) a drug-sensitive uncommitted progenitor cell compartment (2) three transit compartments, and (3) a circulating neutrophil compartment with feedback mechanism. The troxacitabine affected the proliferation of sensitive progenitor cells through an inhibitory E_{max} model. The model parameters were estimated using the MCPEM algorithm that was implemented in a parallel computing platform consisting of a single computer equipped with a quad-core INTEL central processor unit.
Results and conclusions The mechanism-based PK/PD model developed using parallelized MCPEM method adequately describes the complex relationship between the exposure and absolute neutrophil counts in troxacitabine-treated patients with cancer. The simulation results suggested that the less frequent dosing schedule of troxacitabine used currently in clinical studies was associated with less incidence of neutropenia compared to more frequent dosing schedule.

Keywords Troxacitabine · Pharmacokinetics · Pharmacodynamics · Model · Phase I study · Cancer

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Introduction

Troxacitabine (β-L-OddC, BCH-4556, Troxatyl) is a novel unnatural L-nucleoside analogue with a broad range of antitumor activity in preclinical in vitro and in vivo models [15]. Similar to the related natural D-nucleoside analogues such as cytarabine and gemcitabine, troxacitabine produces cytotoxic activity mainly by incorporating troxacitabine triphosphate into DNA resulting in complete DNA chain termination due to the absence of a hydroxyl group in the dioxolone ring of the L-nucleoside [14]. However, unlike its natural D-nucleoside analogues, troxacitabine L-nucleosides are resistant to catabolism by cytidine deaminase, which is an important inactivation pathway for many nucleoside analogues [11, 14]. In several clinical studies, troxacitabine given via various dosing schedules generated partial responses in patients with renal cell carcinoma and refractory myeloid leukemia, and it produced principal toxicities of neutropenia, skin rash, and hand-foot syndrome [8, 13]. The pharmacokinetics of troxacitabine in patients with cancer are best characterized by a

three-compartment linear PK model, and the population mean value for systemic clearance was 9.1 L/h [19]. However, no data on using the PK/PD model to characterize the relationship between the PK and hematologic toxicities for the troxacitabine in patients with cancer have been reported to date.

Currently, most population PK/PD models have been developed using the nonlinear mixed-effect (NLME) method. However, the development of the mechanism-based complex population PK/PD model using the NLME method is a very time- and labor-intensive process. Recent advancement of new NLME methodologies and computing technologies makes it feasible to substantially decrease the time required to construct a complex mechanism-based population PK/PD models for model-based drug development [1, 16, 18]. Among the new NLME methodologies, Monte-Carlo Parametric Expectation–maximization (MCPEM) algorithm is particularly well suited for high-power computing because the most computation demanding steps of the algorithm in obtaining model parameter for each individual subjects can be calculated independently using separate computing unit [1, 21]. This important characteristic makes MCPEM an ideal NLEM method that can take full advantage of the new parallel computing power to improve the efficiency of complex population PK/PD model development.

The objectives of the present study were to develop a mechanism-based PKPD in describing troxacitabine-induced neutropenia in patients with cancer using a parallelized Monte-Carlo Parametric Expectation–maximization (MCPEM) estimation method.

Method

Data

Thirty-one patients with advanced solid malignancies were treated with cisplatin as a 1-h intravenous infusion followed by troxacitabine 30-min intravenous troxacitabine infusion on day 1 every 28 days at the following cisplatin/troxacitabine (mg/m^2) dose levels: 50/4.8, 75/4.8, 50/6.4, 75/6.4, and 75/8.0 [20]. Plasma samples for troxacitabine pharmacokinetic analysis were obtained during cycle 1 before dosing and at 0, 0.25, 0.5, 1, 2, 4, 8, 24, 48, 72, and 168 h after the end of the 30-min intravenous infusion of troxacitabine. Plasma samples were analyzed for troxacitabine at Phoenix International Life Science, Inc. (Saint-Laurent, Quebec) and using a liquid chromatography in tandem with mass spectrometry method validated over the concentration ranges of 0.6–100 ng/mL. Routine laboratory studies including complete blood cell counts were performed pretreatment and weekly. The absolute neutrophil count (ANC) data of patients after receiving granulocyte colony-stimulating factor (C-GSF) were excluded from the data analysis. The study was approved by the institutional board of Cancer Therapy and Research Center at San Antonio and Joe Arrington Cancer Research and Treatment Center at Lubbock, TX. All patients gave written informed consent according to federal and institutional guidelines.

A total of 727 PKPD samples from 31 subjects were included in the analysis. Sixteen of those subjects were men. The study population had a median age of 61 years (range 20–73). All subjects had a history of prior chemotherapy before entering the study. Myelosuppression, particularly neutropenia, was the principal toxicity of the troxacitabine/cisplatin combination. Neutropenia of grade 3 and 4 severity occurred in 34 of the 77 treatment courses and was dose-limiting toxicity in five treatment courses. The average duration of the study period for PD samples collection was 417 days (range 127.2–1,738), and the average number of PD samples per subject was 12.5.

Model development

A mechanism-based PK/PD model was used to characterize the plasma troxacitabine concentration–time profiles and time course of ANC following troxacitabine administrations [9, 17]. A three-compartment linear PK model was used to describe the troxacitabine concentrations data, and the mass balance equations for this model are given in the following equations:

$$\frac{dX_1}{dt} = -\frac{CL}{V_1}X_1 - \frac{Q_1}{V_1}X_1 - \frac{Q_2}{V_1}X_1 + \frac{Q_1}{V_2}X_2 + \frac{Q_2}{V_3}X_3 \quad (1)$$

$$\frac{dX_2}{dt} = \frac{Q_1}{V_1}X_1 - \frac{Q_1}{V_2}X_2 \quad (2)$$

$$\frac{dX_3}{dt} = \frac{Q_2}{V_1}X_1 - \frac{Q_2}{V_3}X_3 \quad (3)$$

where X_1 represents the amount of troxacitabine in the central compartment after intravenous administration, X_2 and X_3 represent amount of troxacitabine in the peripheral compartments, CL is the systemic clearance of the troxacitabine from the central compartment, V_1 is the distribution volume of the central compartment, Q_1 and Q_2 are the inter-compartmental clearance, and V_2 and V_3 are the distribution volume of troxacitabine in peripheral compartments.

The PD model was constructed to mimic the physiologic processes and consists of a stem/progenitor cell compartment (S), three transit compartments with maturing cells (M_1, M_2 and M_3), and the circulating neutrophil compartment (N) (Fig. 1) [10]. The generation of the new stem/

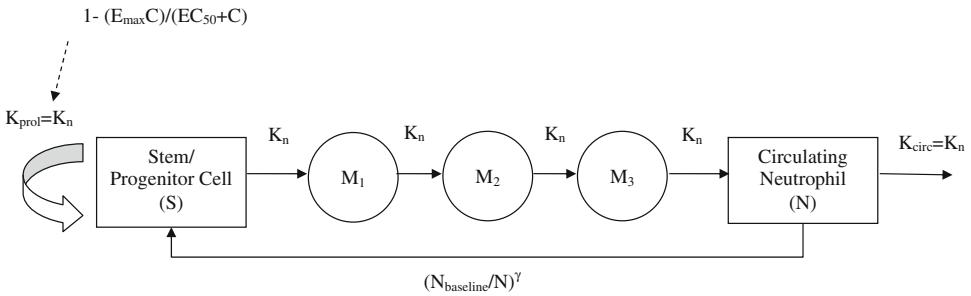


Fig. 1 The mechanism-based neutrophil cell proliferation model with feedback used in the pharmacokinetic/pharmacodynamic analysis. k_{prol} proliferation rate constant of stem/progenitor cells, k_n maturation rate constant, k_{circ} elimination rate constant of circulating neutrophil, M_1–M_3 maturation compartments 1–3, E_{max} $(C)/(EC_{50} + C)$ inhibitory function of troxacitabine concentrations on the proliferation of the stem/progenitor cells where C is the drug concentrations in the central compartment ($C = X_1/V_1$), $(N_{baseline}/N)^{\gamma}$ feedback mechanism that is a function of baseline neutrophil and the neutrophil at any given time

progenitor cells (S) is assumed to be dependent on the (1) number of the stem/progenitor cells in the compartment (i.e., self-renewal or mitosis) which is governed by the first-order proliferation rate constant (k_{prol}) and (2) the feedback mechanism from the circulating neutrophil cells $(N_{baseline}/N)^{\gamma}$. The feedback loop was used to describe the rebound phenomena and to maintain homeostasis of circulating neutrophils. The differential equations of the PD model are written as follow:

$$\frac{dS}{dt} = k_{prol} S\left(1 - \frac{E_{max} \times C}{EC_{50} + C}\right)\left(\frac{N_{baseline}}{N}\right)^{\gamma} - k_n S \quad (4)$$

$$\frac{dM_1}{dt} = k_n S - k_n M_1 \quad (5)$$

$$\frac{dM_2}{dt} = k_n M_1 - k_n M_2 \quad (6)$$

$$\frac{dM_3}{dt} = k_n M_2 - k_n M_3 \quad (7)$$

$$\frac{dN}{dt} = k_n M_3 - k_{circ} N \quad (8)$$

The drug concentrations in the central compartment ($C = X_1/V_1$) are assumed to inhibit the proliferation rate of stem/progenitor cells through an inhibitory E_{max} model, E_{max} $C/(EC_{50} + C)$. In the transit maturing compartment, it is assumed that the loss of cells is only into the next compartment via transit rate constant (K_n). At steady state, $dS/dt = 0$, and therefore, $k_{prol} = k_n$. To minimize the number of parameters to be estimated, it was assumed in the modeling that $k_{circ} = k_n$. The average time it takes for a stem/progenitor cells to mature and appear in the systemic circulation as neutrophil is described by mean transit time (MTT) which was defined as MTT $= (n + 1)/k_n$, where n is the number of transit compartment [9]. Hence, the initial conditions at time $= 0$ prior to drug administration are $S = M_1 = M_2 = M_3 = N =$ baseline ANC values.

Model evaluation and simulation

The ability of the final model to describe the PK/PD data was evaluated by a visual predictive check. In addition, the predictive performance of the model in describing observed ANC was assessed by statistics of minimum observed absolute neutrophil counts (ANC_{min}). The 10th, median, and 90th percentile were calculated, and the probability that the observed statistics is less than the simulated statistics (Ppc) was calculated from 1,000 simulated trials [12, 26].

The final model was used to investigate the incidence of neutropenia associated with different troxacitabine dosing regimens. ANC-time profiles of 1,000 subjects after the administration of troxacitabine at the same dose level but on a different dosing schedule (i.e., 0.96 mg/m^2/day for 5 days every 21 day vs. 4.8 mg/m^2 every 21 days) were simulated and compared.

Data analysis and computing platform

Data were analyzed by the nonlinear mixed-effects modeling method utilizing the Monte Carlo Parametric Expectation Maximization (MCPEM) algorithm implemented in S-ADAPT software (version 1.56). The details of the MCPEM algorithm have been presented elsewhere [1, 21]. Briefly, a two-stage hierarchical nonlinear mixed effect model is used to find the set of mean population parameters μ and population variance matrix Ω that best describes the observed data. In the MCPEM algorithm, final population parameters μ and Ω were obtained by first evaluating the conditional mean $\overline{\theta_i}$ and conditional variance $\overline{B_i}$ for each subject using fixed values of μ and Ω (the expectation step E) according to Eqs. 9 and 10, and then followed by evaluating updates to μ and Ω using Eqs. 11 and 12 (the maximization step M) [23].

Expectation (E) step:

$$\overline{\theta i} = \frac{\int_{-\infty}^{+\infty} \theta p(yi, \theta|\mu, \Omega)\mathrm{d}\theta}{\int_{-\infty}^{+\infty} p(yi, \theta|\mu, \Omega)\mathrm{d}\theta} \quad (9)$$

$$\overline{Bi} = \frac{\int_{-\infty}^{+\infty} \left(\theta - \overline{\theta_i}\right)\left(\theta - \overline{\theta_i}\right)' p(yi, \theta|\mu, \Omega)\mathrm{d}\theta}{\int_{-\infty}^{+\infty} p(yi, \theta|\mu, \Omega)\mathrm{d}\theta} \quad (10)$$

Maximization (M) step:

$$\mu = \frac{1}{m}\sum_{i=1}^{m} \overline{\theta_i} \quad (11)$$

$$\Omega = \frac{1}{m}\sum_{i=1}^{m} \left(\overline{\theta i} - \mu\right)\left(\overline{\theta i} - \mu\right)' + \frac{1}{m}\sum_{i=1}^{m} \overline{Bi} \quad (12)$$

m represented total number of subjects in the analysis. The E and M steps were repeated until μ and Ω no longer change. At this point, final population parameters μ and Ω that best describes the data were obtained [23]. In MCPEM, the Monte-Carlo integration method is used to evaluate $\overline{\theta_i}$ and $\overline{B_i}$ during the expectation step [1].

The PK/PD model was fitted to the data simultaneously. Interindividual variability among the parameters was assumed to be log-normally distributed. Intraindividual variability of PK and ANC were modeled with proportional and poisson error according to Eqs. 13 and 14, respectively [4].

$$\text{Proportional error model: } y_{ij} = yp_{ij} + yp_{ij} \times \varepsilon_{ij,\text{prop}} \quad (13)$$

$$\text{Poissonerror model: } y_{ij} = yp_{ij} + \left(yp_{ij}\right)^{1/2} \times \varepsilon_{ij,\text{poi}} \quad (14)$$

where y_{ij} and yp_{ij} are the jth measured and model-predicted values, respectively, for the ith individual, and $\varepsilon_{ij,\text{prop}}$ and $\varepsilon_{ij,\text{poi}}$ denote the proportional and poisson residual intraindividual random errors distributed with zero means and variances σ^2_{prop} and σ^2_{poi}.

The parallel computing platform was developed in a single computer equipped with Intel Core 2 Quad Core Q6600 CPU, a Windows XP Pro SP3 operating system and Compaq Digital Fortran Compiler (ver 6.6C). The MCPEM algorithm in the S-ADAPT program (version 1.56) was written in Visual Fortran, using the professional Compaq Visual Fortran compiler 6.6C.

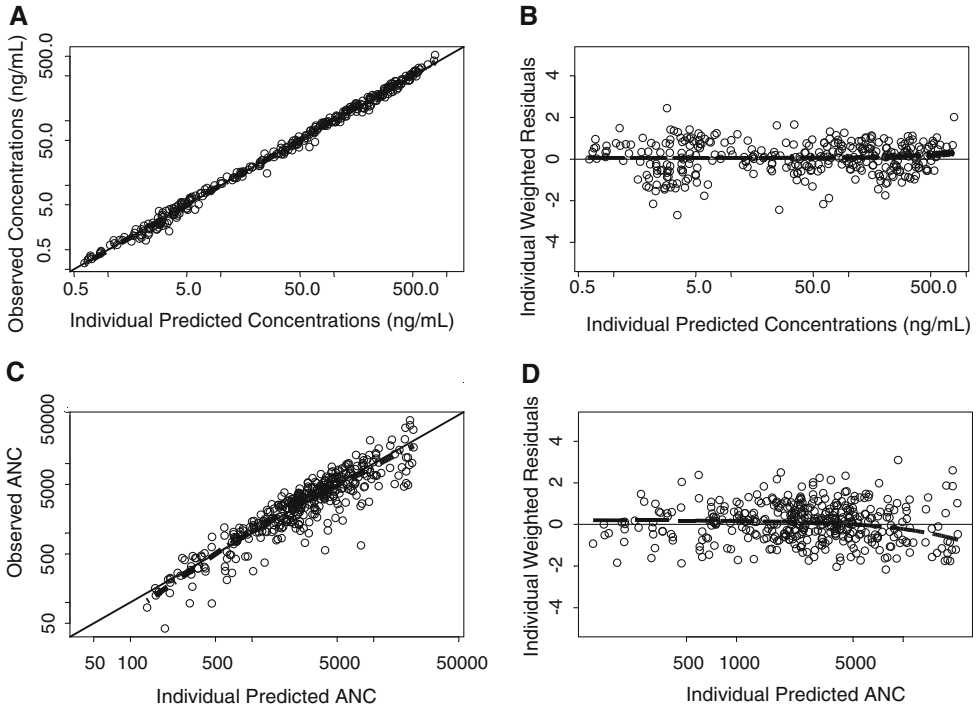
To discriminate between two nested models, a difference in an objective function of greater than 7.9 (1 degree of freedom), which corresponds to a significant level of $P < 0.005$ was used.

Results

An integrated mechanism-based PK/PD model was developed to describe the relationships between the troxacitabine drug exposures and changes in absolute neutrophil counts (ANC) in troxacitabine/cisplatin-treated patients with cancer. The original model was fitted simultaneously to the PK/PD data using the MCPEM estimation method implemented in a parallel computing platform.

During the model development process, the interindividual variability of the $E_{\max}$ in the base model was removed from the base model because (1) this parameter was very small and poorly estimated and (2) removal of this parameter did not result in a statistically significant increase ($\Delta\text{OBJ} < 7.9$, $P > 0.005$) in the objective function. Attempts to improve the fit by incorporating covariance terms in the final model were unsuccessful as most of the included covariance terms were poorly estimated (CV > 50%) mainly due to small number of subjects ($N = 31$) included in the analysis. Therefore, the final structural model was identical to the original model except the interindividual variability of $E_{\max}$ was removed from the final model. In the final PK/PD model, the plasma troxacitabine concentration–time profiles were best described by a three-compartment linear PK model. Figure 2a includes individual predicted versus observed troxacitabine concentration data for all patients. Generally, there was good agreement between the individual predicted and the observed plasma concentrations of troxacitabine. In addition, diagnostic plots (Fig. 2b) of the final PK model identified no systematic bias. Representation plots of observed and individual predicted plasma concentrations–time data for troxacitabine in four patients are shown in Fig. 3a–d, again confirming that the final PK model reasonably described the observed data. The estimated pharmacokinetic parameters are presented in Table 1. The population mean (typical) value of systemic clearance (CL) was 8.59 L/h. The central volume of distribution V_1 was 15.9 L. The inter-compartmental clearances were 5.90 and 14.8 L/h, respectively. The typical volumes of the peripheral tissues were 287 and 23.8 L, respectively. The population variance of the final PK parameters ranged from 0.085 (29.1% CV) to 0.191 (43.7% CV).

The mechanism-based PD model was used to describe the ANC-time profiles after troxacitabine administration. As shown in Fig. 4a–d, the model described the observed ANC-time data reasonably well. In addition, diagnostic plots (Fig. 2c–d) of the final model identify no major systematic bias. The estimated PD parameters are presented in Table 1. The typical values of PD parameters were N_{baseline} 6108 cells/mm^3, MTT 147 h, γ 0.205, $E_{\max}$ 0.772, EC_{50} 1.67 ng/mL, and were determined with good precision (% SE < 50) with the highest percent standard error being 19.7%. The population variance of the final PD parameters ranged from 0.058 (23.1% CV) to 0.748 (86.5% CV) and were estimated with good precision (% SE < 50).



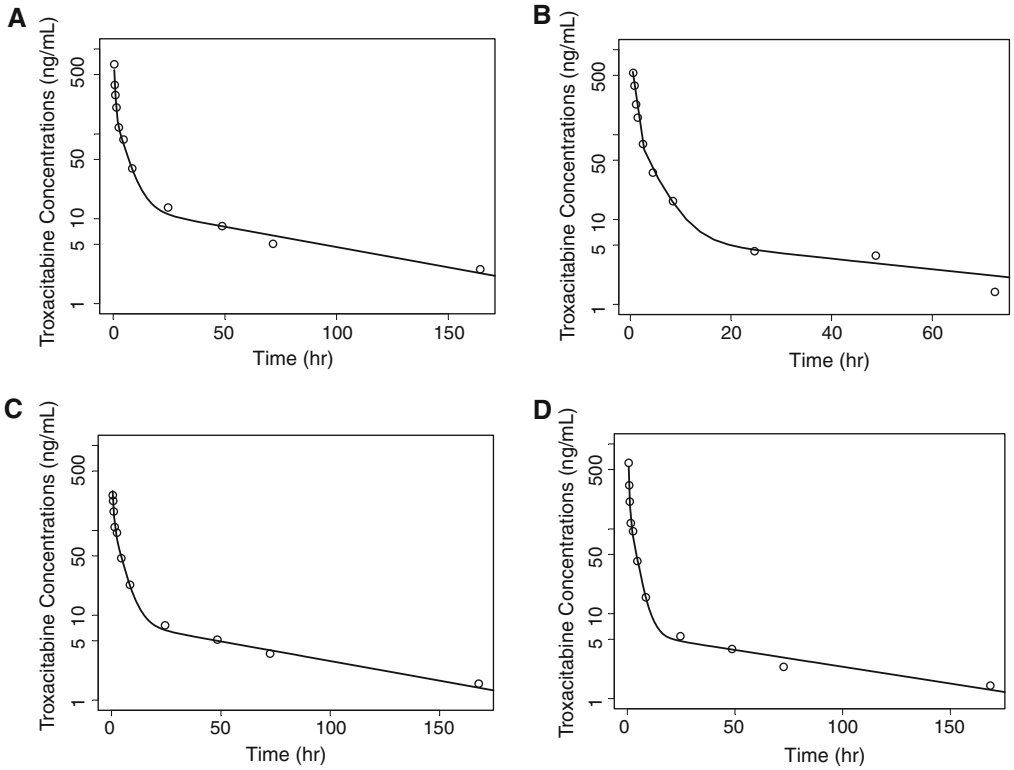


Fig. 2 Model diagnostic plots. **a** Individual predicted versus observed troxacitabine concentrations, **b** individual weight residual versus individual predicted troxacitabine concentrations, **c** individual predicted versus observed ANC, and **d** individual weighted residual versus individual predicted ANC

Fig. 3 Randomly selected individual pharmacokinetic-time profiles and model prediction. *Open circle* observed troxacitabine concentrations; *solid line* model predicted troxacitabine concentrations

Figure 5 displays the visual predictive performance of the final PK/PD model, which indicated that the model adequately described the time courses of troxacitabine concentrations and its effects on ANC. The results of the quantitative predictive check for minimum ANC (ANC_{min}) are shown in Fig. 6. The observed median, 10th and 90th

Table 1 Final parameters' estimates from the PK/PD model

Parameter	Population mean (% SE)[a]	Interindividual variability (% SE)[b]
PK		
CL (L/h)	8.59 (5.4)	0.085 (26.6)
V_1 (L)	15.9 (8.5)	0.147 (33.4)
Q_1 (L/h)	5.90 (5.7)	0.074 (35.7)
V_2 (L)	287 (9.2)	0.191 (32.2)
Q_2 (L/h)	14.8 (9.3)	0.114 (46.7)
V_3 (L)	23.8 (9.5)	0.190 (32.8)
σtroxacitabine[c]	0.165 (6.4)	–
PD		
$N_{baseline}$ (cells/mm^3)	6,108 (10.2)	0.258 (28.7)
MTT (h)	147 (5.1)	0.058 (31.2)
E_{max}	0.772 (1.2)	–
EC_{50} (ng/mL)	1.67 (19.7)	0.748 (34.8)
γ	0.205 (9.2)	0.133 (36.5)
σANC[d]	0.423 (4.4)	–

[a] Percent of standard error of the parameter estimate

[b] Expressed as population variance

[c] Random residual (intraindividual) variability of PK model

[d] Random residual (intraindividual) variability of PD model

percentiles of ANC_{min} were well within the corresponding distributions calculated from the simulated trials, suggesting that the model can provide an adequate description of the ANC_{min} after troxacitabine administration.

ANC-time profiles of 1,000 subjects after the administration of troxacitabine at the same dose level but on a different dosing schedule were simulated using the final model, and the results are shown in Fig. 7. Despite significant overlap between two simulated profiles, troxacitabine administered at lower dose with more frequent dosing intervals (0.96 mg/m^2/day for 5 days every 21 days) produced more prolonged ANC suppression. The simulated subjects who received more frequent dosing schedule also experienced a higher incidence of grade 3 or greater neutropenia (ANC $<$ 1,000 cells/mm^3) anytime during treatment (59.1% vs. 43.2%) compared to subjects who received less frequent dosing.

Discussions

This is the first reported study to use the mechanism-based PK/PD model in describing absolute neutrophil counts-time profiles in troxacitabine-treated patients with cancer. The model was developed using a novel parallelized MCPEM estimation method implemented in a parallel computing platform environment within a single computer.

The developed mechanism-based population PK/PD model adequately described the complex relationship between the drug exposure and absolute neutrophil counts after troxacitabine administration in patients with cancer. During an early exploratory analysis, several models consisting of one-, two-, and three-compartment PK models and E_{max} and sigmoidal E_{max} models in the PD components

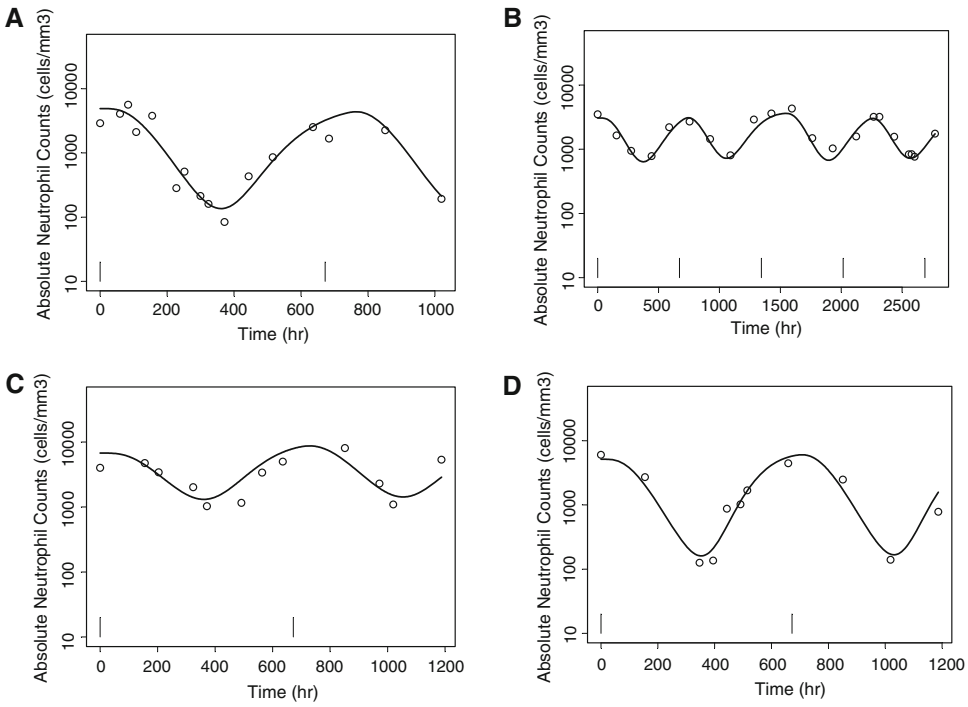


Fig. 4 Individual pharmacodynamic-time profiles and model prediction. *Open circle* observed absolute neutrophil counts; *solid line* model predicted absolute neutrophil counts. *Vertical line* time of troxacitabine dosing

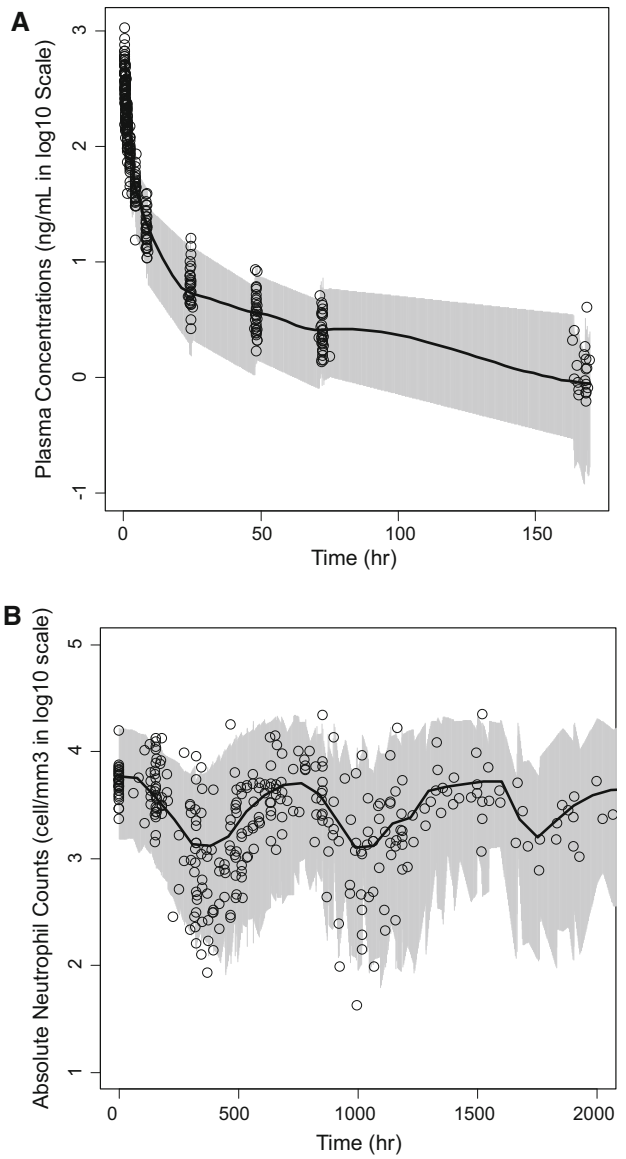


Fig. 5 Visual predictive check of the final PKPD model. *Open circle* observed PK or PD; *solid line* LOESS smoothed model simulated median values; *shaded area* 90% confidence interval of the simulated values

were developed and fitted to PK/PD data simultaneously. The three-compartment PK model with E_{max} model in the PD components was selected as the best model for the PK data based on results of likelihood ratio test and inspection of the standard diagnostic plots (data not shown). During the model development, several residual errors models (proportional, additive, mixed proportional and additive, and poisson error) were tested. Based on the results from the likelihood ratio test, parameter estimates and visual inspection of the diagnostic plots, proportional error, and poisson error models were selected to describe the residual variability of the PK and PD models, respectively.

The typical troxacitabine clearance in the final model is 8.59 L/h, which is comparable to the 9.1 L/h obtained from the covariate-free population PK model reported by Lee et al. [19]. One of the primary toxicities associated with single-agent troxacitabine administration is neutropenia [8, 13]. The troxacitabine mechanism–based PD model was developed based on the model introduced by Frieberg et al. [9, 10] to describe the time-course of absolute neutrophil counts following myelosuppressive chemotherapy administration. Parameters in the mechanism-based PD model are either system- or physiological-based (i.e., $N_{baseline}$, MTT, and γ) or drug-effect related (i.e., E_{max} and EC_{50}). Since the system parameters characterize the physiology of hematopoiesis in patients with cancer, they should be consistent across various cancer patient populations. Estimates for $N_{baseline}$, MTT and γ from our analyses were consistent with those reported by others [9, 17] and comparable to the postmitotic transit times of neutrophil in healthy volunteers (6.6 days, 158 h) [5]. The typical values of drug-related parameters were 0.772 and 1.67 ng/mL for E_{max} and EC_{50}, respectively. The low EC_{50} values relative to the drug exposure achieved at clinical troxacitabine doses does suggests that at the same dose level, troxacitabine administered via different schedules may have different effects on the ANC-time profiles (schedule-dependent drug-related toxicity). The model-based simulation results using two commonly used troxacitabine dosing schedules in clinical studies [3, 8] suggested that troxacitabine administered at lower dose with more frequent dosing intervals produced more prolonged ANC suppression, thus supporting the less frequent dosing schedule of troxacitabine used currently in clinical studies. This is probably due to the time of troxacitabine exposure above the EC_{50} value is shorter for less frequent dosing interval compared to more frequent dosing of troxacitabine and this allows more times for neutrophil to recover before the next scheduled doses (data not shown). The troxacitabine-induced neutropenia resulted from a complex interaction between the neutrophil biology and drug effects on the sensitive stem/progenitor cells. Ideally, troxacitabine should be given less frequently as a short IV bolus dose to allow the drug concentrations fall quickly below the critical exposure level for neutrophil to recover before next schedule doses. Therefore, the frequent-dosing regimens (such as weekly dosing) were expected to produce higher incidence of neutropenia because the next scheduled doses were given before the damaged stem/progenitor cells (from previous dose) had time to recover. This hypothesis was supported by the results from simulation study using the final model. Simulated subjects who received once weekly dosing (1.6 mg/m^2 weekly) had a much lower ANC-time profiles compared to subjects who received less frequent dosing (4.8 mg/m^2 every 21 days) (Fig. 8). In addition, the

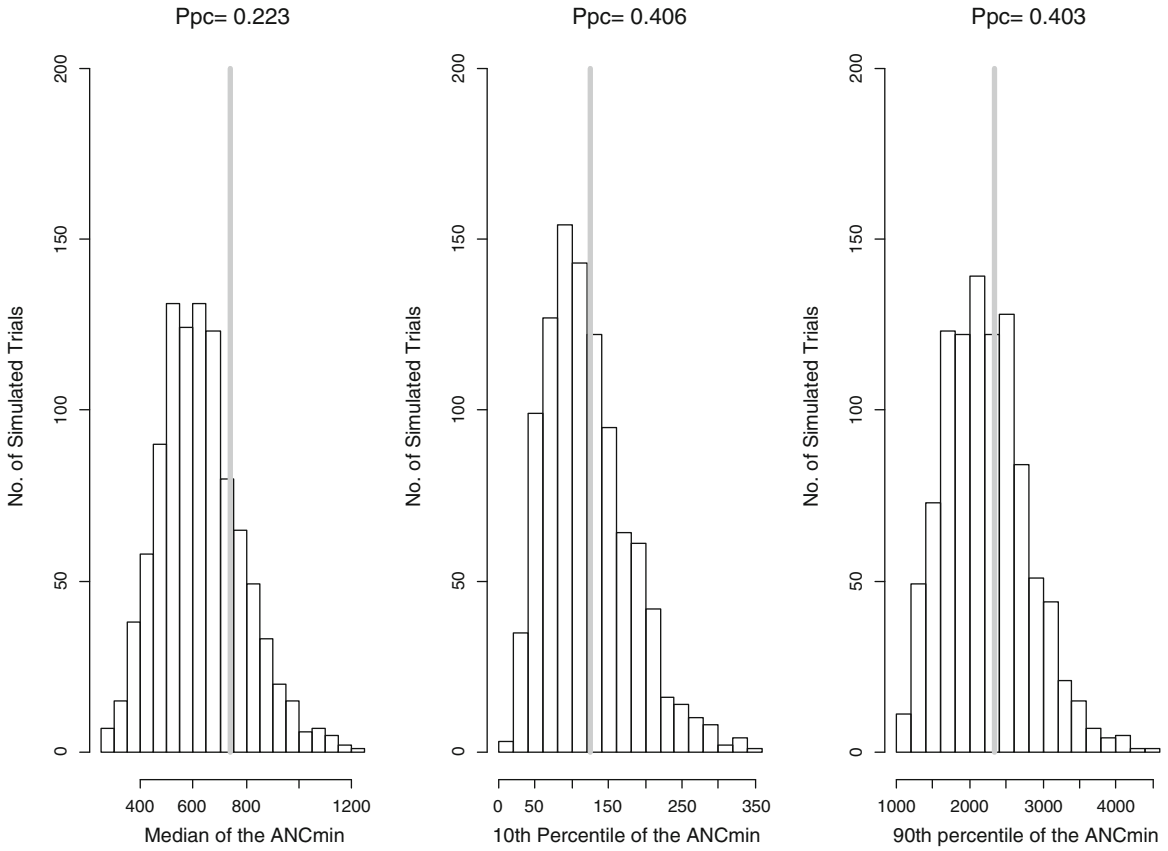


Fig. 6 Predictive performance check of the final PK/PD model. The model adequately predicted median and variability (10 and 90th percentiles) of the minimum ANC values. *Ppc* probability of simulated trials ($N = 1{,}000$) greater than the observed statistics. The *vertical lines* show values of observed minimum ANC values

simulated subjects who received weekly dosing experienced a much higher incidence of grade 3 or greater neutropenia (ANC $< 1{,}000$ cells/mm^3) anytime during treatment (93.3% vs. 43.2%) compared to subjects who received troxacitabine once every 21 days.

One potential drawback of our analysis is that the mechanism-based PD model of troxacitabine was developed using the data from patients receiving both troxacitabine and cisplatin combination. Neutropenia was the principal dose-limiting toxicity in patients with cancer treated with troxacitabine alone and patients in the first course of treatment experienced a high frequency of hematologic events at doses above 1.2 mg/m^2/day [8]. Although cisplatin has a potential to produce a transient and mild myelosuppression [6, 22, 24], neutropenia of less than 2,000 cells/mm^3 is rare with intermittent doses of 50–60 mg/m^2 [22]. Hence, it is reasonable to assume that the neutropenia observed in the troxacitabine/cisplatin-treated patients with cancer is mainly due to the myelosuppressive effects of troxacitabine. However, the combination of cisplatin and troxacitabine did produce dose-limiting myelosuppression at lower dose of troxacitabine than single-agent doses, suggesting that the cisplatin may potential the myelosuppression effects of the troxacitabine in cancer [20]. Therefore, the relationships between the troxacitabine drug exposure and ANC of troxacitabine in our model may be potentially confounded by the use of combination chemotherapy. Further analysis using data from patients treated with single-agent troxacitabine is needed to better understand the relationships between troxacitabine exposure and ANC-time profiles in patients with cancer.

During the PK/PD model development, NLME models are used to obtain the maximum likelihood estimation of the population PK/PD parameters from the observed data. However, maximum likelihood estimation in the NLME model presents a substantial challenge because the likelihood function cannot typically be expressed in closed form. Therefore, several different approximations of the likelihood function have been proposed for use in population PK/PD analysis, particularly the linear approximation methods such as FO and FOCE methods in NONMEM [2]. Because these methods are based on approximation of the true likelihood function, the population PK/PD parameters obtained from these methods are not true maximum likelihood estimators and they may contain considerable errors [1, 7, 18]. This has motivated the use of the method that

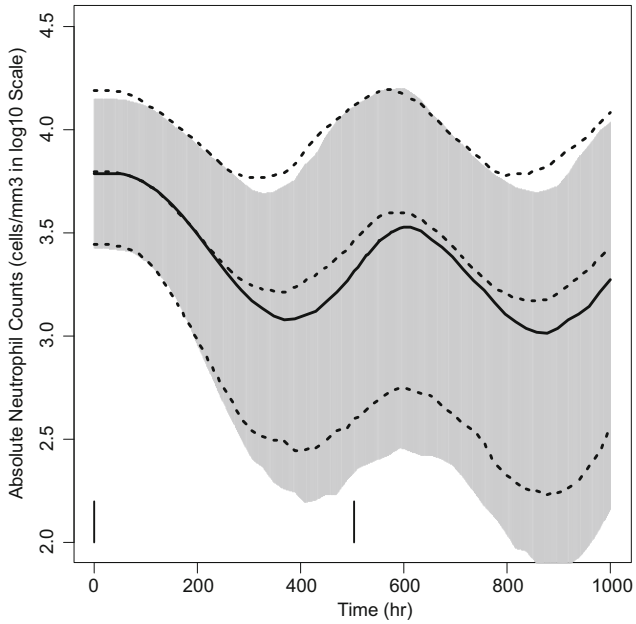


Fig. 7 Model predicted ANC-time profiles in the 1,000 simulated subjects after administration of **a** troxacitabine 0.96 mg/m^2/day given as 30 min IV infusion for 5 days every 21 days, or **b** 4.8 mg/m^2 given as 30 min IV infusion every 21 days (*broken line*). *Solid line* and *gray shading area* median and 90% quantile plots of the subjects who received troxacitabine dose for 5 days every 21 days. *Dashed lines* median and 90% quantile plots of the subjects who received single troxacitabine dose every 21 days. *Vertical line* troxacitabine administration times. The BSA value of 1.73 m^2 is assumed for the all simulated subjects

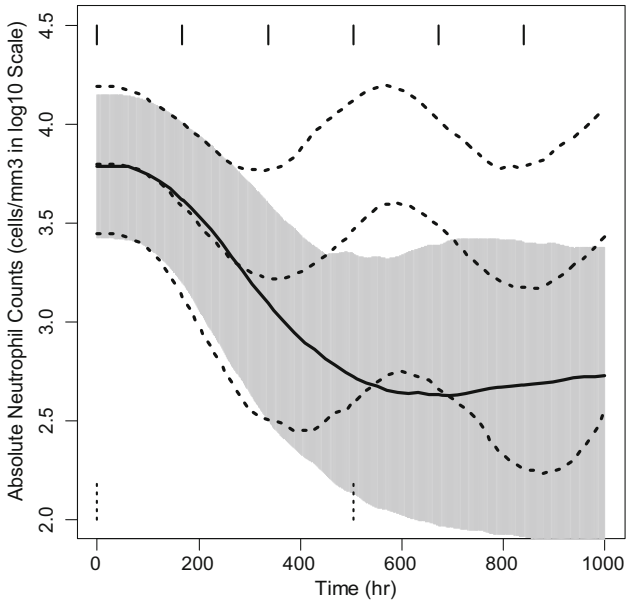


Fig. 8 Model predicted ANC-time profiles in the 1,000 simulated subjects after administration of **a** troxacitabine 1.6 mg/m^2/day given as 30 min IV infusion weekly, or **b** 4.8 mg/m^2 given as 30 min IV infusion every 21 days (*broken line*). *Solid line* and *gray shading area* median and 90% quantile plots of the subjects who received weekly troxacitabine dose. *Dashed lines* median and 90% quantile plots of the subjects who received single troxacitabine dose every 21 days. *Dashed vertical lines* troxacitabine administration times for dosing regimens with once every 21 days. *Solid vertical lines* troxacitabine administration times for weekly dosing regimens. The BSA value of 1.73 m^2 is assumed for the all simulated subjects

can estimate the exact likelihood function, specifically, the Monte Carlo EM algorithm such as MCPEM and SAEM [1, 18, 23, 25]. Traditionally, the mechanism-based PK/PD models were developed using these NLME algorithms implemented on a single computer platform, e.g., the population parameters were obtained by analyzing all the individual subjects sequentially from the population in a single computer. Due to the model complexity and number of analyzed subjects in the population, model development using this approach can be very time and resource intensive.

Recent advances in computing technology make it possible to build an affordable high power parallel computing platform for developing a complex mechanism-based population PK/PD model for drug development. Among the NLME algorithm available, MCPEM is especially well-suited for distributed parallel computing because the most computational intensive E-step of the MCPEM algorithm for each individual subjects can be analyzed independently. In this paper, we built a parallel computing platform for MCPEM using a single computer equipped with a powerful Intel Core 2 QUAD Core Q6600 CPU. The Intel Core 2 QUAD Core Q6600 CPU is an advanced processor featuring four individual processing cores, and the use of more than one core pre processor allows the individual cores to perform separate tasks, making this particular CPU especially well suited for developing a cost-effective parallel computing tool for analyzing the complex population PK/PD models using MCPEM algorithm.

In this study, we attempt to fit the PKPD data with the model described in this paper using the first-order conditional estimation with interaction (FOCEI) in NONMEM VI software [2] with the same initial parameter estimates identical to those used in the MCPEM algorithm. However, the NONMEM program would repeatedly terminated without completing the analysis. After multiple attempts to change the initial population parameters and system parameters, the PK/PD model developed using FOCEI in NONMEM program finally achieved convergence after more than 2 days (3,220.5 min) but still failed to obtain the COVARIANCE step in calculating the standard error of the parameter estimates. Compared to FOCEI method in NONMEM, the parallelized MCPEM method is more efficient and took about 12 min to complete the analysis. In addition, it is relatively more stable and requires no restarts in developing this complex mechanism–based PK/PD model. A detail simulation study to compare the

performance of traditional FOCEI and MCPEM method in complex PK/PD data analysis is ongoing in order to confirm the preliminary findings in this study.

In summary, an innovative MCPEM-based parallel computing platform was used to develop the mechanism-based PK/PD model that can describe the complex relationship between the drug exposure and absolute neutrophil counts after troxacitabine administration in patients with cancer. The simulation results suggested that the less frequent dosing schedule of troxacitabine was associated with less incidence of neutropenia compared to more frequent dosing schedule, thus supporting the current dosing regimens used in clinical studies.

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