Cancer Chemother Pharmacol (2009) 63:469–476
DOI 10.1007/s00280-008-0760-4

ORIGINAL ARTICLE

A Bayesian population PK–PD model for ispinesib/docetaxel combination-induced myelosuppression

Steven J. Kathman · Daphne H. Williams · Jeffrey P. Hodge · Mohammed Dar

Received: 20 February 2008 / Accepted: 9 April 2008 / Published online: 29 April 2008

Abstract
Purpose Ispinesib, a kinesin spindle protein inhibitor, blocks assembly of a functional mitotic spindle, leading to G2/M arrest. Docetaxel promotes tubulin assembly into microtubules while inhibiting microtubule de-polymerization leading to mitotic arrest. Prolonged (≥5 days) Gr 4 neutropenia and/or febrile neutropenia were the observed dose-limiting toxicities with both agents. Both agents are substrates and inhibitors of CYP3A4; thus, the potential for a drug–drug interaction exists. The goal was to fit a Bayesian population PK/PD model to characterize the relationship between the ispinesib/docetaxel combination and absolute neutrophil counts (ANC).
Methods Escalating doses of docetaxel (60–75 mg/m^2) were administered over 1 h followed by a 1-h infusion of escalating doses of ispinesib (8–12 mg/m^2) on a 21-day schedule. At least 3 pts were treated at each dose level. Limited PK samples were obtained. ANC were measured weekly on days 1, 8, 15, and 22. More ANC samples were taken from some subjects. The PK properties of ispinesib and docetaxel, and the relationship of PK with ANC were investigated using nonlinear mixed-effects models and Bayesian methods. With a limited dataset, informative prior distributions for the model parameters were needed. These prior distributions were formed using information from a previous study for ispinesib, and from the literature for docetaxel.
Results Twenty-four pts were treated in this study. The PK of ispinesib and docetaxel were well characterized by a two-compartment model and a three-compartment model, respectively. There is no obvious PK interaction between ispinesib and docetaxel. The model for ANC consisted of a proliferating compartment, three transit compartments that represented maturation, and a compartment of circulating blood cells. This ANC model has been used previously for ispinesib given as monotherapy, and for other chemotherapeutic drugs in the literature. Using Bayesian methods, the model was successfully fit for the PK of both compounds and the PD simultaneously.
Conclusions The PK/PD model developed for ispinesib/docetaxel, may be used to examine different schedules, doses, and infusion times of both agents. Bayesian methods allow for the use of prior information available for the model parameters.

Keywords Myelosuppression · Pharmacokinetics · Pharmacodynamics · Absolute neutrophil count · Bayesian methods

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Introduction

Kinesin spindle protein (KSP) is a novel molecular target for anti-cancer therapy.

Kinesin spindle protein is necessary in the initial stages of mitosis for the separation of spindle poles and eventual formation of distinct daughter cells. Inhibition of KSP results in formation of monopolar spindles within a single cellular envelope and has induced apoptosis, or programmed cell death in non-clinical studies. Ispinesib is a novel KSP inhibitor that blocks assembly of a functional mitotic spindle by inhibiting spindle pole separation.

A drug that targets KSP offers the potential for broader anti-tumor activity than that observed with currently available chemotherapeutics. Additionally, a KSP inhibitor

may avoid the complications of neurotoxicity demonstrated by anti-tubulin agents (i.e., taxanes and vinca alkaloids) which is caused by their inherent interference with tubulin function in nondividing cells. Similar to many other anti-proliferative drugs, ispinesib is expected to have manageable dose-limiting toxicities (e.g., myelosuppression) resulting from effects on normal proliferating tissues.

Docetaxel, a member of the taxane family, has demonstrated activity in both advanced breast and non-small cell lung cancers. It is currently approved as monotherapy for second-line treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy and for locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. In addition, docetaxel is approved in combination with cisplatin for the first-line treatment of patients who are chemotherapy naive, with unresectable, locally advanced or metastatic non-small cell lung cancer.

Ispinesib and docetaxel inhibit distinct mitotic targets during the M phase of the cell cycle which may reflect their different safety profiles. While ispinesib inhibits the initial stage of mitotic entry, spindle pole separation; docetaxel blocks the cell's ability to break down the mitotic spindle by inhibiting microtubule depolymerization. Docetaxel binds reversibly to the beta subunit of tubulin, promoting microtubule assembly and stability, thereby blocking the cell cycle in mitosis. Both docetaxel and ispinesib arrest cells in mitosis, resulting in subsequent cellular death.

Preclinical data with docetaxel and ispinesib demonstrates synergy in a MX-1 tumor mouse xenograft model. The addition of ispinesib (30 mg/m^2) to docetaxel (30 and 90 mg/m^2) resulted in greater tumor growth delay compared to docetaxel alone (30 and 90 mg/m^2). No evidence of tumor regrowth was seen in mice treated with both ispinesib and docetaxel.

Myelosuppression is the major dose-limiting toxicity for many chemotherapeutic drugs. It is an important consideration in the development of novel cytotoxics in oncology, especially for targeted antimitotic drugs, where the dose-limiting toxicity is likely to be myelosuppression. The optimization of dose/administration schedule early in development of such agents (and combinations of agents) by establishing the relationship between drug concentration and myelosuppression could greatly aid in the identification of a potential therapeutic window. Pharmacokinetic–pharmcodynamic (PK–PD) modeling of absolute neutrophil counts (ANCs) has been performed separately for ispinesib [8] and docetaxel [5] previously. The goal of the present analysis is to fit a population PK–PD model to characterize the relationship between the ispinesib–docetaxel combination and ANCs. The model is fit using Bayesian Markov Chain Monte-Carlo (MCMC) methods. More comprehensive data on safety and other clinical effects were recorded and will be reported elsewhere [2].

Methods

Study design

A first time in human, phase I open label, non-randomized, dose-escalating study evaluating ispinesib and docetaxel given in combination has been completed. Escalating doses of docetaxel (60–75 mg/m^2) were administered over 1 h followed by a 1-h infusion of escalating doses of ispinesib (8–12 mg/m^2) on a 21-day schedule. Doses were escalated in successive three-patient cohorts. Cohorts were expanded for dose-limiting toxicities and following the determination of the maximum-tolerated dose, to better characterize the safety of the combination. Sparse sampling was done for PK, yielding four samples for docetaxel and three samples for ispinesib. Blood samples were taken prior to starting both the docetaxel and ispinesib infusion, immediately at the end of the docetaxel infusion, and at 2, 4–6, and 24-h after the start of the docetaxel infusion. ANCs were assessed weekly on days 1, 8, 15, and 22 (before the start of the second cycle). More frequent assessments were carried out if clinically indicated.

Analysis methods

The models described in the following sections are non-linear hierarchical models that were fit using Bayesian MCMC techniques. If θ_i and φ_i represent vectors of individual PK and PD parameters, respectively, then it was assumed that they follow distributions with population parameters Θ and Φ, respectively. The parameters Θ and Φ were then assigned vague or weakly informative prior distributions depending on the prior information available. The Bayesian analysis involved the estimation of the joint distribution of all parameters conditional on the observed data: $p(\theta, \varphi, \Theta, \Phi|\text{PK and PD data})$, where θ and φ denote collections of all individual specific PK and PD parameters, respectively. Generating random samples from the joint posterior distribution allows the marginal distribution of each parameter to be completely characterized. More detailed information on Bayesian analyses of PK–PD models may be found in Lunn et al. [11] and Duffull et al. [4]. The model was fit to the data using WinBugs v1.4.3 [12] with the Pharmaco interface and WBDiff, which together make up PKBugs v2.0. Convergence was assessed both visually, by examining trace and running quartile plots, and formally using the Brooks–Gelman–Rubin diagnostic [7] available in WinBugs.

PK models

Ispinesib

The time course of ispinesib was assumed to follow a two-compartment model, based on previous work [8]. Subjects were dosed based on mg/m^2, but the total dose administered in mcg was used in the modeling with body surface area used as a covariate.

For the two-compartment model, it was assumed that an individual's concentration at a given time point followed a normal distribution with mean η_{ij} and variance τ_{ij}, where i and j index the individual and time, respectively. The mean η_{ij} is a function of time, length of infusion, and the following parameters: the elimination clearance (CL_i), the volume of distribution for the central compartment (V_{1i}), the volume of distribution for the peripheral compartment (V_{2i}), and the intercompartmental clearance (Q_i). The variance τ_{ij} was set equal to $\sigma_a^2 + \sigma_p^2\eta_{ij}^2$, where σ_a^2 and σ_p^2 represent the additive and proportional variance terms, respectively.

Now let θ_i be a vector containing the log-transformed PK parameters for the ith individual [$\ln(CL_i)$, $\ln(Q_i)$, $\ln(V_{1i})$, $\ln(V_{2i})$], then θ_i was assumed to follow a multivariate normal distribution with mean Θ and variance–covariance matrix Σ. Body surface area, centered at its mean, was used as a covariate for $\ln(Q_i)$ and $\ln(V_{1i})$. Parameters associated with the mean vector (Θ) were then assigned an informative multivariate normal prior distribution with the mean vector and a variance–covariance matrix based on previous work [8]. In particular, the posterior distributions from the previous modeling were taken as the prior distributions here. The inverse of Σ was assigned using a vague prior Wishart distribution according to the PK Bugs manual (http://www.winbugs-development.org.uk/), using an initial estimate for the inter-individual coefficient of variation of 30% for the pharmacokinetic parameters. Since the least informative proper Wishart prior distribution is being used for the inverse of Σ, the data should have an important role in the forming of the posterior distribution; thus the model is not too sensitive to the initial estimate of 30%. The variance terms σ_a and σ_p were assigned half-normal prior distributions (the absolute value of a normal random variable with mean equal to zero and variance equal to 1). Given the results from the previous work [8], this is still fairly uninformative.

Docetaxel

Based on previous work in the literature [1, 3, 10], the time course of docetaxel was assumed to follow a three-compartment model. The three-compartment model is similar to the two-compartment model described above, with a few notable differences. The mean η_{ij} is now a function of time, length of infusion, and the following parameters: the elimination clearance (CL_i), the volume of distribution for the central compartment (V_{1i}), the volume of distribution for each of the two peripheral compartments (V_2) and (V_{3i}), and the two intercompartmental clearances (Q_{2i}) and (Q_{3i}). Note that the volume of one of the peripheral compartments (V_2) is being estimated for the population, and not for each individual since this leads to an improvement in the convergence of the model. Estimating V_2 for each individual was attempted, but the autocorrelation in the generated samples was very high, making convergence difficult to assess and achieve. Ordering constraints are needed for the volumes to ensure that the model is identifiable [11]. This requires $\theta_i = [\ln(CL_i), \ln(Q_{2i}), \ln(Q_{3i}), \ln(V_{1i}), \ln(V_2), \ln(V_{3i} - V_2)]$. Body surface area and age, both centered at their means, were considered as covariates for $\ln(CL_i)$. Parameters associated with the mean vector (Θ) were then assigned an informative multivariate normal prior distribution with the mean vector and a variance–covariance matrix based on previous work [1]. In particular, the mean vector was based on previous results [1], except for the slopes on age and body surface area, where they were set to zero. The variance–covariance matrix contained inflated variances (set equal to 1). This was done to allow the data to have more influence on the final results. The inverse of Σ was assigned using a vague prior Wishart distribution according to the PK Bugs manual (http://www.winbugs-development.org.uk/), using an initial estimate for the inter-individual coefficient of variation of 30% for the pharmacokinetic parameters. A Student's t distribution with 4 df was used here for the docetaxel concentrations as opposed to the normal distribution since visual inspection of the data revealed that there were a few potential outliers in the dataset.

PK–PD model

A semi-mechanistic model [5, 6] was used to describe the impact of the ispinesib–docetaxel combination on ANC. The model has also been used or discussed elsewhere in the literature [8, 9, 14–16]. The model (shown in Fig. 1) consisted of a proliferating compartment (Prol), three transit compartments (Transit1, Transit2, Transit3) that represented the stepwise maturation of leukocytes within the bone marrow, and a compartment of circulating blood cells (Circ). A negative feedback mechanism $(Circ_0/Circ)^{\gamma}$ from circulating cells on proliferating cells was included to describe the rebound of the cells (including an overshoot compared to the baseline: $Circ_0$). The differential equations were written as

$$\mathrm{dProl}/\mathrm{d}t = k_{\mathrm{Prol}}\mathrm{Prol}\left(1 - E_{\mathrm{Drug}}\right)(\mathrm{Circ}_0/\mathrm{Circ})^{\gamma} - k_{\mathrm{tr}}\mathrm{Prol}$$
$$\mathrm{dTransit1}/\mathrm{d}t = k_{\mathrm{tr}}\mathrm{Prol} - k_{\mathrm{tr}}\mathrm{Transit1}$$
$$\mathrm{dTransit2}/\mathrm{d}t = k_{\mathrm{tr}}\mathrm{Transit1} - k_{\mathrm{tr}}\mathrm{Transit2}$$
$$\mathrm{dTransit3}/\mathrm{d}t = k_{\mathrm{tr}}\mathrm{Transit2} - k_{\mathrm{tr}}\mathrm{Transit3}$$
$$\mathrm{dCirc}/\mathrm{d}t = k_{\mathrm{tr}}\mathrm{Transit3} - k_{\mathrm{Circ}}\mathrm{Circ}.$$

In the model, k_{tr}, k_{Prol}, and k_{Circ} represent the maturation rate constant, the proliferation rate constant, and the cell elimination rate constant, respectively. The rate constants $k_{\mathrm{tr}} = k_{\mathrm{Prol}}$ since dProl/d$t = 0$ at steady state, and is also assumed to be equal to the rate constant k_{Circ} to reduce the number of parameters to be estimated. The effect of the drug concentration in the central compartment on the proliferation rate was modeled with a linear function: $E_{\mathrm{Drug}} = \beta_{\mathrm{isp}}{*}\mathrm{Conc}_{\mathrm{isp}} + \beta_{\mathrm{doc}}{*}\mathrm{Conc}_{\mathrm{doc}}$ for a given individual, where Conc represents the drug concentrations in the central compartments and the βs are the slope parameters.

It was then assumed that the ANC value for subject i at time j followed a Student's t distribution with mean $\mu_{(\mathrm{ANC})ij}$, variance v_{ij}, and 4 df. A Student's t distribution was used here given its robust properties, including protection against the influence of outliers. The mean $\mu_{(\mathrm{ANC})ij}$ is obtained from the solution of the differential equations (Circ compartment), and is a function of the following: an individual's slopes β_is for ispinesib and docetaxel, an individual's baseline value $\mathrm{Circ}_{(0)i}$, an individual's mean transit time $\mathrm{MTT}_i = (n_{\mathrm{c}} + 1)/k_{(\mathrm{tr})i}$ where n_{c} is the number of transit compartments, the exponent part of the feedback mechanism γ (modeled for the population as a whole, not separately for each individual), and an individual's concentration of ispinesib and docetaxel at time j (simultaneously being modeled from the two and three-compartment models described above). The variance v_{ij} was set equal to $\sigma^2_{(\mathrm{ANC})\mathrm{a}} + \sigma^2_{(\mathrm{ANC})\mathrm{p}}\mu^2_{(\mathrm{ANC})ij}$, where $\sigma^2_{(\mathrm{ANC})\mathrm{a}}$ and $\sigma^2_{(\mathrm{ANC})\mathrm{p}}$ represent the additive and proportional variance terms, respectively.

$\ln(\beta_{i,\ \mathrm{isp}})$, $\ln(\beta_{i,\ \mathrm{doc}})$, $\ln(\mathrm{Circ}_{(0)i})$, and $\ln(\mathrm{MTT}_i)$ were assumed to be mutually independent and follow normal distributions with means $\mu_{\beta(\mathrm{isp})}$, $\mu_{\beta(\mathrm{doc})}$, μ_{Circ0}, μ_{MTT} and variances $\sigma^2_{\beta(\mathrm{isp}),}$ $\sigma^2_{\beta(\mathrm{doc}),}$ $\sigma^2_{\mathrm{Circ0}}$, σ^2_{MTT}, respectively. The parameters μ_{Circ0}, μ_{MTT}, and γ are considered system-related parameters, and should be consistent across different drugs, and thus were given weakly informative prior distributions. Friberg et al. [5] examined what would happen if the system-related parameters were fixed, or set to particular values. The prior distributions selected here for μ_{Circ0} and μ_{MTT} are centered (mean) at the recommended values for fixing the parameters: $\ln(5 \times 10^9/\mathrm{L})$ and ln(125 h), respectively. The SD for the prior distributions of μ_{Circ0} and μ_{MTT} were chosen to be 0.25, which is considerably larger than that obtained from the posteriors in the previous modeling of ispinesib alone [8]. This was done to allow the current data to have more influence over the results. The exponent γ was given a half-normal [using normal (0,1)] prior distribution, which again is consistent with the results observed in the literature [5, 8] where it ranged from 0.160 to 0.230. The mean $\mu_{\beta(\mathrm{isp})}$ is specific to ispinesib and was thus given an informative prior distribution (normal with mean $= -4.57$ and SD $= 0.25$), based on previous modeling [8], but with an inflated SD. The mean $\mu_{\beta(\mathrm{doc})}$ is specific to docetaxel and was thus given an informative prior distribution (normal with mean $= -4.61$ and SD $= 0.25$), based on previous modeling [5]. The SDs $\sigma_{\beta(\mathrm{isp})}$, $\sigma_{\beta(\mathrm{doc})}$, σ_{Circ0}, and σ_{MTT} were given uniform (0,1) prior distributions, which are weakly informative here. The terms $\sigma_{(\mathrm{ANC})\mathrm{a}}$ and $\sigma_{(\mathrm{ANC})\mathrm{p}}$ were assigned half-normal prior distributions (absolute value of a normal random variable with mean equal to zero and variance equal to one).

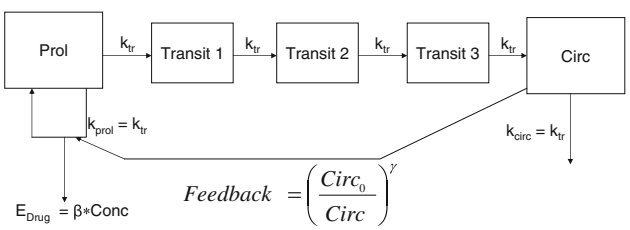

Fig. 1 Semi-mechanistic model of drug-induced myelosuppression

Results

Twenty-four patients (21 males, 3 females), with a median age of 61.2 years were treated between June 2004 and June 2005. Table 1 contains a summary of the demographic

Table 1 Summary of demographics ($n = 24$)

Parameter	Value
Age (years)	
Median and range	61.2 (41–76)
Weight (kg)	
Mean and range	82.0 (58–118)
SD	14.1
Height (cm)	
Mean and range	172.8 (162–185)
SD	6.1
Body surface area (m^2)	
Mean and range	1.98 (1.65–2.42)
SD	0.19
Body mass index (kg/m^2)	
Mean and range	27.4 (21–37)
SD	3.8

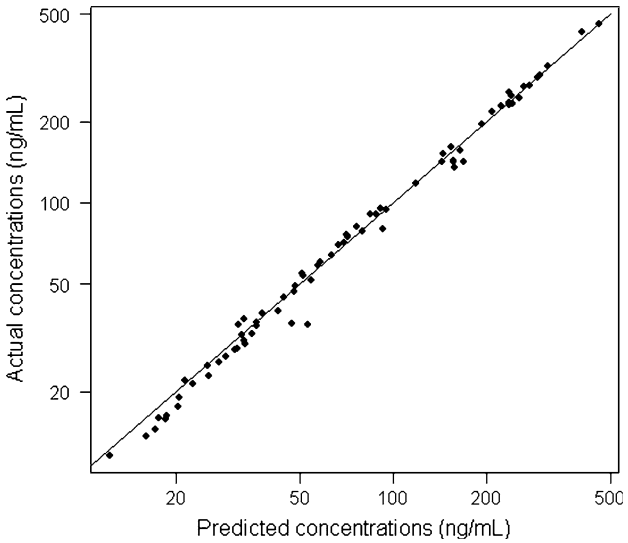

Fig. 2 Comparison of observed ispinesib concentrations (ng/mL) and concentrations predicted using the mean of the posterior distribution and a two-compartment model

characteristics. More information on the background of the patients enrolled is reported elsewhere [2].

Two chains with different starting values were used to help assess convergence. We took 20,000 burn-ins and then recorded every second sample out of the next 30,000 iterations to reduce the autocorrelation in the Markov chain, and based on all the computations on the resulting 30,000 (15,000 per chain) posterior samples. The Markov chains converged fast (within the first 10,000 iterations) and mixed well.

The two-compartment model appears to fit the ispinesib concentration data well (Fig. 2). Figure 2 shows the actual PK concentrations versus the predictions from the two-compartment model, using the means of the posterior distributions as the predictions. Table 2 presents characteristics of the posterior distributions for the population parameters from the two-compartment model. Most of the PK parameters were consistent with what was seen previously and used as prior distributions here. The largest difference is in the population mean for clearance (natural log), which has a posterior mean and median of about 1.97 here, compared to 1.83 seen previously [8]. The additive term for the error model was also larger in this study. The intersubject coefficients of variation for the PK parameters, based on medians of posterior distributions for the diagonal elements of the variance–covariance matrix, were 51, 29, 69, and 48% for CL, Q, V_1, and V_2, respectively.

The three-compartment model appears to fit the docetaxel concentration data well (Fig. 3). Figure 3 shows the actual PK concentrations versus the predictions from the three-compartment model, using the means of the posterior distributions as the predictions. Table 3 presents characteristics of the posterior distributions for the population parameters from the three-compartment model. The final distributions were fairly close to what was expected and used as prior distributions for the population parameters. The clearance (intercept on the log scale, which would correspond to a person at the mean BSA and Age since they were centered) was slightly higher (3.71 vs. 3.61) than previously observed [1]. Age was not a significant covariate here, which could be due to the limited amount of data that is available. The intersubject coefficients of variation for the PK parameters, based on medians of posterior distributions for the diagonal elements of the variance–covariance matrix, were 29, 60, 46, 42, and 43% for CL, Q_2, Q_3, V_1, and $V_3 - V_2$, respectively.

The PK–PD model was simultaneously fit for the drug concentrations for each compound, and the ANCs using the model described above in "PK–PD model". Figure 4 shows the observed ANC versus the predictions from the model, again using the means of posterior distributions for predictions. Figure 5 shows the actual and predicted ANC values for three representative subjects in the trial, at different dose levels. Table 4 presents some characteristics of the posterior distributions for the population parameters. The mean for the natural log of the MTT was slightly lower here compared to the mean of the prior distribution, but was only slightly lower than that observed for docetaxel alone (84 vs. 88.7 h [5]). The baseline ANC (Circ_0) was higher compared to its prior mean, and was higher compared to the compounds analyzed in Friberg et al. [5] as well as by others [8, 9, 14–16].

Table 2 Summary of posterior distributions for population parameters in the PK model for ispinesib

Parameter	Mean	SD	Median	2.5%	97.5%
Mean for ln(CL(L/h))	1.96	0.081	1.97	1.80	2.12
Intercept for mean of ln(Q(L/h))	4.20	0.073	4.20	4.06	4.35
Slope (BSA(m^2)) for mean of ln(Q(L/h))	0.45	0.22	0.45	0.008	0.88
Intercept for mean of ln(V_1(L))	2.96	0.097	2.96	2.77	3.15
Slope (BSA(m^2)) for mean of ln(V_1(L))	0.95	0.24	0.95	0.48	1.42
Mean for ln(V_2(L))	5.28	0.077	5.28	5.13	5.43
σ_a (ng/mL)	0.81	0.62	0.68	0.03	2.31
σ_p (%)	15	3	15	9	21

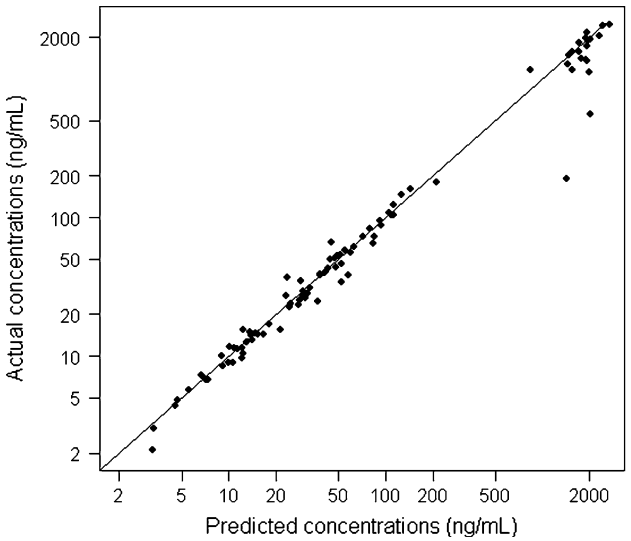

Fig. 3 Comparison of observed docetaxel concentrations (ng/mL) and concentrations predicted using the mean of the posterior distribution and a three-compartment model

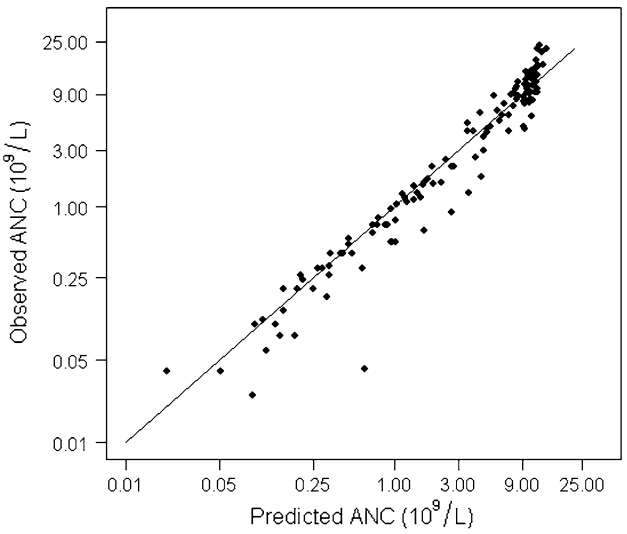

Fig. 4 Comparison of observed ANC (10^9/L) and ANC predicted using the mean of the posterior distribution

The subjects in this trial seemed to have relatively large baseline ANC values (median = 10.4×10^9/L, 25–75% = 8.1×10^9–13.0×10^9/L). The baseline ANC values for most of the other trials are around 5 or 6×10^9/L. The slope parameters for docetaxel and ispinesib were both also higher compared to their prior means. This could be due to the higher baseline ANC values, and the fact that the nadirs were similar compared to the other trials.

Discussion

A Bayesian approach was used to fit the models as opposed to the frequentist approach (obtaining maximum likelihood estimates and confidence intervals) that is most commonly used. The Bayesian approach readily allows for the incorporation of prior knowledge, which exists for most of the parameters since the models have been fit previously for the two compounds when given alone. Incorporating prior knowledge may be useful in cases where the data are sparse, as was the case for the drugs concentrations and ANC for the subjects in this trial. A Bayesian analysis also expresses uncertainty about a parameter in terms of probability, and thus the probability of a parameter being within a certain region or interval may be discussed. This is not the case for a frequentist analysis where estimates and confidence intervals are usually presented. The Bayesian approach uses Monte-Carlo methods as opposed to some of the more traditional algorithms (e.g., Taylor Series-based approximations for integration and gradient-based maximization algorithms). Though not fully discussed here, more information on Monte-Carlo methods may be found in Robert and Casella [13]. Duffull et al. [4] also gives some indication that Bayesian methods are worth considering for population PK models, partially due to their use of Monte-Carlo algorithms.

Bayesian methods not only allow for the use of prior information, but more importantly, provide substantial scope for extending the specified model, and allow for the

Table 3 Summary of posterior distributions for population parameters in the PK model for docetaxel

Parameter	Mean	SD	Median	2.5%	97.5%
Intercept for mean for ln(CL(L/h))	3.71	0.06	3.71	3.56	3.83
Slope ($BSA(m^2)$) for mean of ln(CL(L/h))	1.17	0.31	1.18	0.55	1.78
Slope [age(years)] for mean of ln(CL(L/h))	0.01	0.006	0.01	−0.003	0.02
Mean of $\ln(Q_2(L/h))$	2.08	0.29	2.09	1.53	2.63
Mean of $\ln(Q_3(L/h))$	2.47	0.13	2.47	2.22	2.72
Mean of $\ln(V_1(L))$	2.10	0.19	2.11	1.72	2.46
Mean of $\ln(V_2(L))$	1.21	0.36	1.16	0.66	2.02
Mean for $\ln(V_3(L) - V_2(L))$	5.10	0.16	5.10	4.80	5.42
σ_a (ng/mL)	0.63	0.48	0.52	0.03	1.79
σ_p (%)	30	5	30	22	41

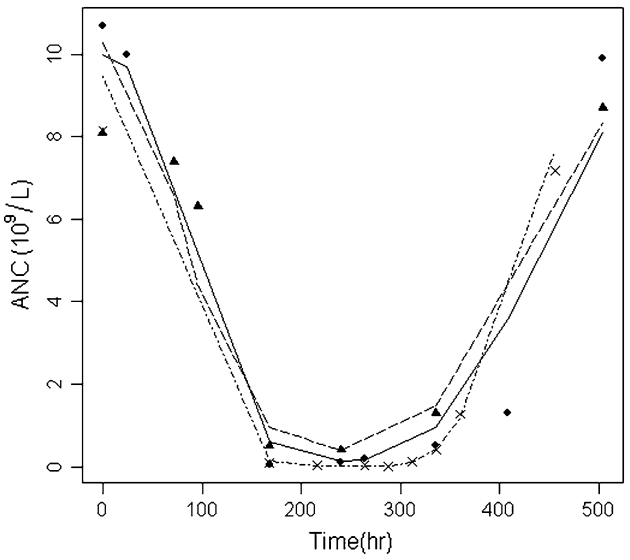

Fig. 5 Plot of observed ANC (10^9/L) (*symbols*) and the predictions from the model (*lines*) versus time in hours for three representative subjects in the trial. The *solid circles* and *solid line* correspond to a subject who received 8 mg/m^2 of ispinesib and 60 mg/m^2 of docetaxel. The *uptriangle* and *dashed line* correspond to a subject who received 10 mg/m^2 of ispinesib and 60 mg/m^2 of docetaxel. The *cross* and *dot-dashed line* correspond to a subject who received 8 mg/m^2 of ispinesib and 75 mg/m^2 of docetaxel

replacement of normality assumptions with other distributions (such as a Student's t distribution) to provide robustness against outliers. A t distribution with four degrees of freedom was chosen for the docetaxel concentrations and the ANC values since there was a concern about potential outliers.

The semi-mechanistic model for ANC, originally described in Friberg et al. [5], adequately describes the neutrophil counts after the administration of ispinesib and docetaxel. The current PK–PD model can be used to simulate expected incidence of clinically significant neutropenia on alternative schedules of ispinesib to better inform future clinical development decisions. This provides information that may be useful in planning trials to examine other schedules or different lengths of infusion. For example, if it is determined that a prolonged exposure may be desirable, then simulations may be performed before conducting the trial to help determine how long the infusion should be, how often the drug should be given, and at what dose to start with to better ensure the safety of the patients, at least in terms of neutropenia. There were no data available to examine the utility or accuracy of this here, but the model did perform well in predicting a different schedule than what was used to generate the data in the case of ispinesib alone [8].

There is some concern over the PD model's ability to separate the effects due to each compound when they are given in combination. In this particular case though, we are also using information from trials where the compounds were given alone. From the prior information available [5, 8], it appears that both compounds have a similar effect on ANCs.

The PK models considered here fit the data for ispinesib very well, and also did well for docetaxel (aside from a couple data points). A previously well established PK model for docetaxel [3] was considered, but was unable to be fit to the current data. The model includes an indicator variable for subjects with elevated liver function tests (alanine amino transferase—ALT and aspartate amino transferase—AST). The indicator variable is used to identify subjects with AST or ALT $>$ 60 IU. In this trial, the maximum ALT was 48 IU and the maximum AST was 42 IU. AST and ALT were examined separately as continuous variables (as covariates for CL), and neither contributed significantly, likely due to the lack of elevated values and limited amount of data. The median of the posterior distributions for slope parameters for AST and ALT were close to zero. Zero was contained within the 25–75% intervals of the posterior distributions. Alpha 1-acid glycoprotein (AAG) was not collected in this study and could not be considered here. Albumin was collected, but

Table 4 Summary of posterior distributions for population parameters in the PD model

Parameter	Mean	SD	Median	2.5%	97.5%
Mean for ln(MTT(hr))	4.43	0.06	4.43	4.30	4.55
SD for ln(MTT(hr))	0.26	0.05	0.25	0.18	0.38
Mean for ln(Circ_0(10^9/L))	2.33	0.07	2.34	2.19	2.46
SD for ln(Circ_0(10^9/L))	0.16	0.07	0.16	0.02	0.32
Mean for ln(Slope) for ispinesib(ng/mL)	−4.41	0.24	−4.40	−4.91	−3.95
SD for ln(Slope) for ispinesib(ng/mL)	0.71	0.19	0.73	0.27	0.99
Mean for ln(Slope) for docetaxel(ng/mL)	−4.13	0.22	−4.12	−4.57	−3.72
SD for ln(Slope) for docetaxel(ng/mL)	0.69	0.16	0.69	0.38	0.98
γ	0.12	0.006	0.12	0.11	0.13
$\sigma_{(\text{ANC})\text{a}}$ (10^9/L)	0.24	0.059	0.24	0.14	0.37
$\sigma_{(\text{ANC})\text{p}}$ (%)	21	2.7	21	16	27

did not contribute significantly, though this could also be due to the limited amount of data in this trial. Previous modeling [3] suggests that liver function test results, AAG, and BSA are the main predictors of docetaxel clearance. These variables should continue to be considered in future modeling exercises involving docetaxel.

The software used to fit these models was WinBugs version 1.4.3 [12] with the WBDiff and Pharmaco add-ons.

Acknowledgments We first thank the patients who took part in this trial for their willingness to participate and contribute to our understanding of these compounds. We also thank the editor and referee(s) for their constructive comments and valuable suggestions. Finally, we thank the developers and contributors of the WinBugs program and the WBDiff and Pharmaco add-ons, all of which are available free of cost.

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