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ORIGINAL ARTICLE

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Clinical application of a semimechanistic-physiologic population PK/PD model for neutropenia following pemetrexed therapy

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Abstract *Purpose*: The objective of these analyses was to examine the effect of variations in the explanatory factors of neutropenic response, identified by semimechanistic-physiologic population pharmacokinetic/pharmacodynamic (PK/PD) modeling, on clinically important features of the absolute neutrophil count (ANC)-time profile (e.g., the nadir of the ANC [NANC], its timing [T_{Nadir}], and the timecourse of recovery [T_{Rec}]). *Methods*: Correlation analyses were used to evaluate the relationship of NANC, T_{Nadir}, and T_{Rec} as a function of overall systemic exposure (AUC) and each of the covariates contained in the population PK/PD model. Simulations using the final PK/PD model were used to generate complete ANC-time profiles. Frequency counts of NANCs from the simulated profiles were used to quantitatively explore differences in the incidence and severity of neutropenia associated with a variety of scenarios (500 mg/m^2 versus 600 mg/m^2, normal vitamin deficiency markers versus elevated vitamin deficiency markers, and body surface area-based versus renal function-based dosing) and to evaluate the effect of individual explanatory factors with respect to neutropenic response. *Results*: Information obtained from correlation analysis and simulations was helpful in quantitatively exploring the impact of dose, exposure, and/or patient characteristics on neutropenic response. The information gained from these simulations provided supportive evidence for the decision to routinely include vitamin supplementation during pemetrexed treatment as a means of managing the risk of severe neutropenia secondary to pemetrexed administration. These techniques also provided information regarding the specific T_{Nadir} and T_{Rec} for inclusion in product labeling and suggested that a 14-day treatment cycle might be feasible for pemetrexed. *Conclusion*: For population PK/PD models, to provide useful information for the practicing clinician or the clinical development team, it is not sufficient to look only at influences of covariates on model parameters. Rather, the modeling results need to be carefully investigated in terms of clinically relevant measures.

Keywords Hematologic toxicity · Neutropenia · Pemetrexed · Alimta · Pharmacodynamics · Semimechanistic-physiologic · Simulation

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Introduction

Pemetrexed is a novel anticancer agent that has recently been approved in combination with cisplatin for treatment of malignant pleural mesothelioma [32] and as single-agent therapy for second-line treatment of non-small cell lung cancer [15]. The recommended pemetrexed dose is 500 mg/m^2 administered as a 10-min intravenous infusion on day 1 of a 21-day cycle. When given in combination with cisplatin, the recommended dose of cisplatin is 75 mg/m^2 infused over 2 h beginning approximately 30 min after the end of pemetrexed administration. To reduce systemic toxicity, patients treated with pemetrexed also receive vitamin B_{12} and folic acid supplementation.

One of the principle toxicities of pemetrexed following single-agent administration [16] is the presence of severe neutropenia (common toxicity criteria [CTC] grade 3 or 4). When absolute neutrophil counts (ANCs) decrease, the incidences of serious adverse events (e.g., serious infection, sepsis, or febrile neutropenia) increase. Therefore, identifying factors associated with a higher rate of severe neutropenia and/or with delayed recovery from severe neutropenia will lead to more effective and safe treatment for patients receiving pemetrexed therapy.

The previous paper [18] described population pharmacokinetic/pharmacodynamic (PK/PD) analyses conducted using a seven-compartment semimechanistic-physiologic model to characterize the depth and timecourse of the neutropenic response to pemetrexed and to identify patient characteristics associated with variability in neutropenic response. The model provides a mathematical representation of the hematopoietic response to drug (Fig. 1, left panel) and was parameterized in terms of clearance (CL), central volume of distribution (V_1), intercompartmental clearance (Q), peripheral volume of distribution (V_2) for the PK component, and baseline absolute neutrophil count (BAS), mean transit time (MTT), a dose stimulus parameter (DS), and a feedback parameter (FP) for the PD portion. Data from eight phase II cancer studies in which patients received pemetrexed 500 or 600 mg/m^2 without vitamin supplementation were included in the analysis [17, 18]. The studies were prospectively designed to include a sparse blood sampling strategy for evaluation using population PK/PD techniques.

The final model included total systemic exposure to pemetrexed (as dose and CL). Blood levels of cystathionine (CYS), homocysteine (HCY), serum albumin (ALB), and total protein (TPR) as well as body surface area (BSA) are included in the model as covariates that significantly affected the neutropenic response to pemetrexed. Therefore, these covariates (associated with the four PD model parameters [BAS, MTT, DS, and FP]), together with dose and CL (i.e., area under the curve [AUC]; total exposure) in the PK portion of the model, are explanatory factors with respect to neutropenic response. Thus, pemetrexed dose, CL, CYS, HCY, ALB, TPR, and BSA significantly affect the overall timecourse and degree of neutropenia following pemetrexed administration.

Results from these population PK/PD analyses using a semimechanistic-physiologic model expressed in terms of covariate relationships relative to model parameters provide only a qualitative understanding of the covariate effects on the ANC-time profile and have limited utility to the practicing physician or to the clinical drug development team. For population PK/PD models to be useful tools in optimizing dosing regimens, it is not sufficient to only look at influences of covariates on model parameters. Rather, the modeling results need to be carefully investigated in terms of clinically relevant measures.

The current paper examines the effect of variations in the explanatory factors of neutropenic response on clinically important features of the ANC-time profile that characterize depth and duration (Fig. 1, right panel), including the nadir of the absolute neutrophil count (NANC), the time of its occurrence relative to drug administration (T_{Nadir}), the timecourse of recovery to a lesser hematologic toxicity grade (recovery times to CTC grade 3 [$T_{\text{Rec,3}}$], grade 2 [$T_{\text{Rec,2}}$], grade 1 [$T_{\text{Rec,1}}$], and grade 0 [$T_{\text{Rec,0}}$]), and the time required to return to baseline ANC ($T_{\text{Rec,b}}$). Simulations based on the PK/PD model were used to quantitatively compare treatment scenarios (500 mg/m^2 versus 600 mg/m^2, normal vitamin deficiency markers versus elevated vitamin deficiency markers, and BSA-based versus renal function-based dosing) and to evaluate the effect of the covariates in the model.

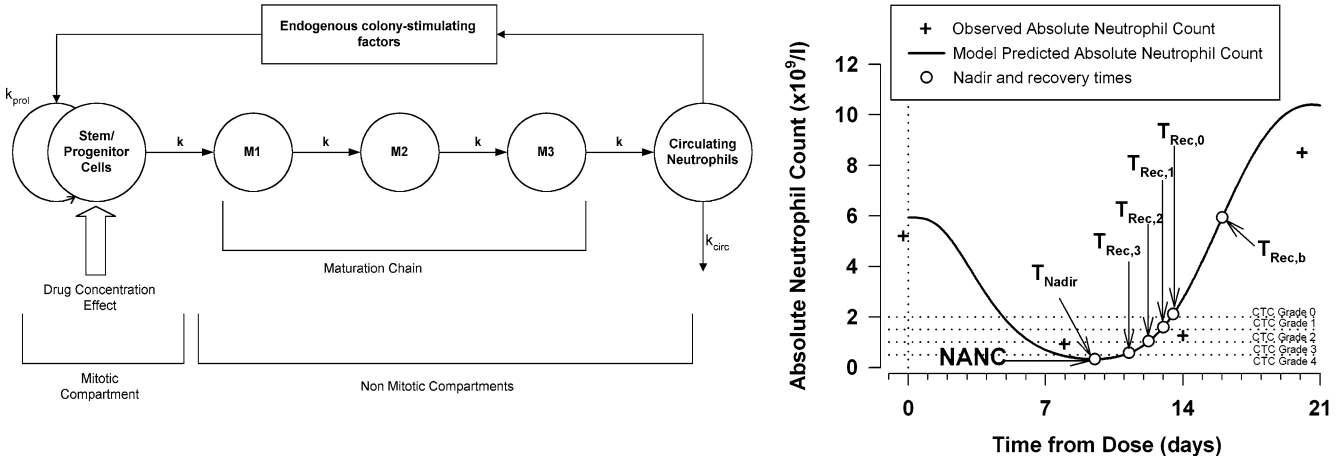

Fig. 1 Neutrophil cell proliferation model with feedback (*left panel*) and clinically relevant aspects of the absolute neutrophil count versus time profile (*right panel*).
Horizontal dashed lines in *right panel* hematologic toxicity grades: CTC grade 1 <2, grade 2 <1.5, grade 3 <1, and grade 4 <0.5

Methods

The NANC, T_{Nadir}, and recovery times were identified from model-predicted ANC-time profiles for 279 patients included in a semimechanistic-physiologic population PK/PD evaluation of neutropenia following pemetrexed administration [18]. Correlation analyses were used to evaluate the relationship of NANC, T_{Nadir}, and T_{Rec} as a function of overall systemic exposure (AUC) and of each of the covariates contained in the population PK/PD model [18]. It should be noted that, although the covariates are not completely independent, the relationships between covariates and response variables were examined separately. Despite this limitation, the strength of the relationships between explanatory and response variables can be examined using this approach.

Simulations incorporating variability were used to generate complete ANC-time profiles for a variety of scenarios: 500 mg/m^2 versus 600 mg/m^2, normal vitamin deficiency markers versus elevated vitamin deficiency markers, and BSA-based versus renal function-based dosing. Simulations were performed using the nonlinear mixed-effect modeling program (NONMEM) (version V) with PREDPP (version V) [3].

The same procedure was implemented to generate the NANC probability distributions used to compare the 500- versus 600-mg/m^2 doses and the "typical" versus elevated vitamin deficiency marker scenarios. For each scenario ("typical" patient treated with 500 mg/m^2, "typical" patient treated with 600 mg/m^2, and patient with elevated vitamin deficiency markers treated with 500 mg/m^2), datasets were created containing five observation records with randomly distributed timepoints per single treatment cycle for each of 500 otherwise identical patients. The dataset also contained additional event records (EVID = 2) inserted at 6-h intervals throughout the evaluation period. For these 500 hypothetical patients, ANC data were generated by Monte Carlo simulation using the final PK/PD model. The simulated data were then evaluated with NONMEM, and the NANCs (IPREDs) were identified from the full profiles. For the 500- and 600-mg/m^2 datasets, absolute dose (i.e., mg) was based on median BSA; covariates and pharmacokinetic parameters were set to their population medians. For the elevated vitamin deficiency marker dataset, a nominal 500-mg/m^2 dose was applied; HCY = 18.1 μmol/l; CYS = 909 nmol/l (which represent the 95th percentiles of patient data used for model development); all pharmacokinetic parameters and remaining covariates were set to their population medians.

Dose-normalized versions of the analysis dataset were used to simulate predicted ANC-time profiles to compare BSA-based and renal function-based dosing (i.e., based on estimated creatinine clearance [5]) for patient characteristics contained in the analysis dataset. The BSA-based dosing was fixed at 500 mg/m^2. The renal function-based dosing was calculated for individual patients to achieve an AUC of 163.7 μg·h/ml, which corresponds to the AUC expected for a "typical" individual (median BSA [1.81 m^2] and median creatinine clearance [CrCL; 96.6 ml/min]) dosed with 500 mg/m^2. Additional event records were included in the dataset at 6-h intervals throughout the evaluation period. Absolute neutrophil count data were generated by Monte Carlo simulation using the final PK/PD model. The simulated data were then evaluated with NONMEM and the NANCs (IPREDs) were identified from the full profiles. Therefore, these simulations represent the patient characteristics and the variability of the original analysis population. Frequency distributions of NANCs from the simulated data were used to quantitatively explore differences in the incidence and severity of neutropenia associated with different scenarios (500 mg/m^2 versus 600 mg/m^2, normal vitamin deficiency markers versus elevated vitamin deficiency markers, and BSA-based versus renal function-based dosing).

Results

Effect of individual explanatory factors on NANC

The relationship between the NANC and each of the explanatory factors (AUC, CYS, HCY, ALB, TPR, and BSA), holding all remaining explanatory factors constant at their central tendency, is illustrated in Fig. 2 (solid curves). These curves represent the central tendency of the relationship (i.e., "typical" values without variability). An increase of two or more CTC grades compared to baseline ANC would be expected as AUC increases from the population median to the population maximum. Serum ALB had only a minimal effect, with an increase of approximately one-half of a CTC grade from the population median to the population minimum. The remaining covariates produced increases of 1 to $1-\frac{1}{2}$ CTC grades, as each was varied individually from their population median value to the population minimum or maximum value associated with a lowering of the NANC. Increased HCY or CYS were associated with a lowering of the NANC.

The open circles in Fig. 2 illustrate the variability in the NANC that is attributable to the explanatory variables other than that indicated on the *x*-axis of a particular graph. The graph for AUC contains the individual patient predictions of the NANC based on the final model for patients and doses contained in the analysis dataset. The covariate plots are population predicted NANCs based on patient characteristics contained in the analysis dataset with exposure (AUC) held constant.

Comparison of the incidence of neutropenia for 500- and 600-mg/m^2 doses

The ANC-time profile for the "typical" patient receiving pemetrexed 500 mg/m^2 or 600 mg/m^2 is shown in Fig. 3.

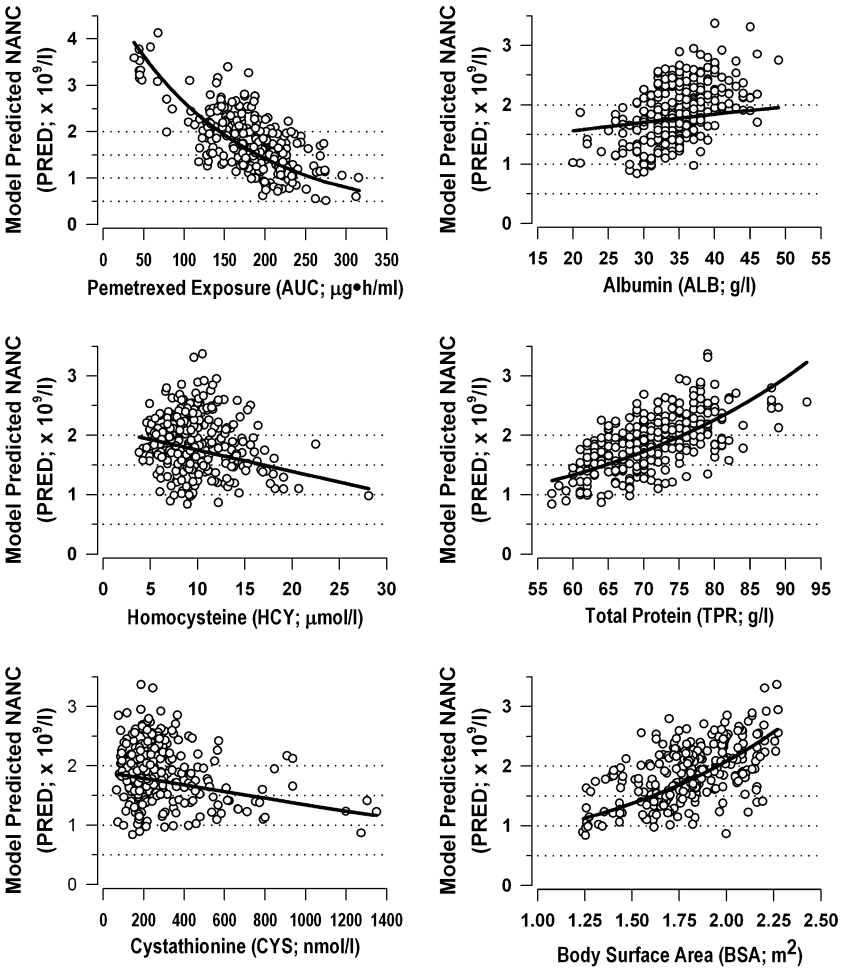

Fig. 2 Final population PK/PD model: AUC-NANC and covariate-NANC (AUC 163.7 µg·h/ml) relationships—simple simulations with covariate effects
horizontal dashed lines hematologic toxicity grades: CTC grade 1 <2, grade 2 <1.5, grade 3 <1, and grade 4 <0.5. *Curves*: Simulations varying specific covariate of interest with all other covariates remaining fixed to their population medians; AUC fixed to 163.7 µg·h/ml (corresponding to [500 mg/m^2] [1.81 m^2]/[92.2 ml/min]) except where varied (*top left panel*). *Open circles*: For AUC, individual predictions (IPREDs) based on analysis results. For covariates, population predictions (PREDs) based on covariate data for treatment cycles contained in the analysis dataset with AUC-normalized doses

The typical NANC was 1.77×10^9/l for the 500 mg/m^2 dose and 1.45×10^9/l for the 600 mg/m^2 dose. Estimates of a predicted posterior frequency distribution of NANC values by hematologic CTC grades, based on simulation using variability estimates from the final population PK/PD model suggested that there would be about a 50% probability that the "typical" patient receiving 500 mg/m^2 pemetrexed would remain at CTC grade 0, but only about a 25% probability that the identical "typical" patient would remain at CTC grade 0 following a 600-mg/m^2 dose. Thus, these distributions showed an increased incidence of neutropenia associated with the higher dose.

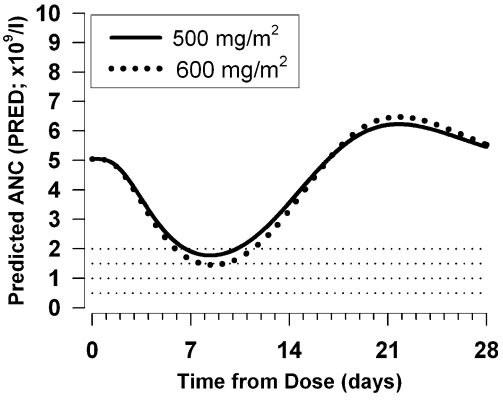

Fig. 3 Final population PK/PD model: comparison of 500- and 600-mg/m^2 doses for a "typical" patient
"Typical" patient: pemetrexed CL 92.2 ml/min; median values for each of the covariates in the final model

Comparison of the incidence of neutropenia for "typical" versus elevated vitamin deficiency markers

The ANC-time profile for a "typical" patient (i.e., holding all explanatory factors constant at their central tendency) compared to an otherwise "typical" patient with elevated CYS and HCY where each received a nominal pemetrexed dose of 500 mg/m^2 is shown in Fig. 4 (top panel). The predicted NANC for the "typical" patient receiving 500 mg/m^2 was 1.77×10^9/l, while the predicted NANC for the patient with elevated CYS and HCY was 0.975×10^9/l. Estimates of predicted posterior frequency distributions of NANC by hematologic CTC grades using simulations are also provided in Fig. 4 (center and bottom panels). These histograms suggest that the probability of patients remaining at

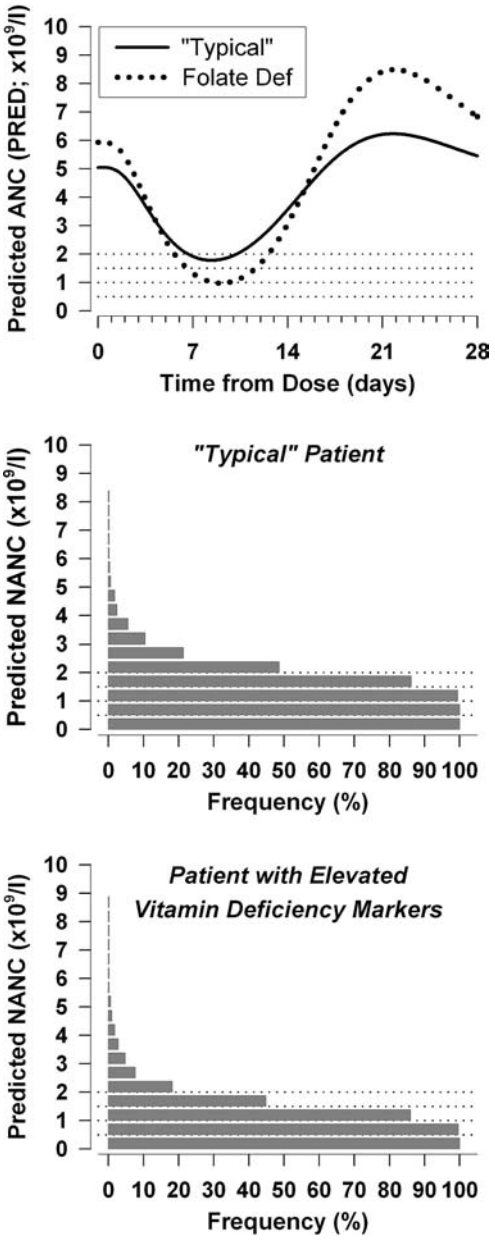

Fig. 4 Final population PK/PD model: effect of elevated vitamin deficiency markers.
top panel ANC-time following pemetrexed administration *center* and *bottom panels* frequency distributions of predicted NANC based on variability estimates from final model (*gray bars* simple frequency; *black bars* cumulative frequency). *Horizontal dashed lines* hematologic toxicity grades: CTC grade 1 <2, grade 2 <1.5, grade 3 <1, and grade 4 <0.5. "Typical" patient: pemetrexed CL 92.2 ml/min; median values for each of the covariates in the final model patient with elevated vitamin deficiency markers: pemetrexed CL 92.2 ml/min; median values for each of the covariates in the final model other than HCY and CYS; HCY = 18.1 μmol/l; CYS = 909 nmol/l which represent the 95th percentiles of patient data used for model development

CTC grade 0 toxicity would decrease from about 50% for "typical" patients to less than 20% for the patients with elevated CYS and HCY. The histograms also show an increased incidence of severe neutropenia associated with elevated CYS and HCY.

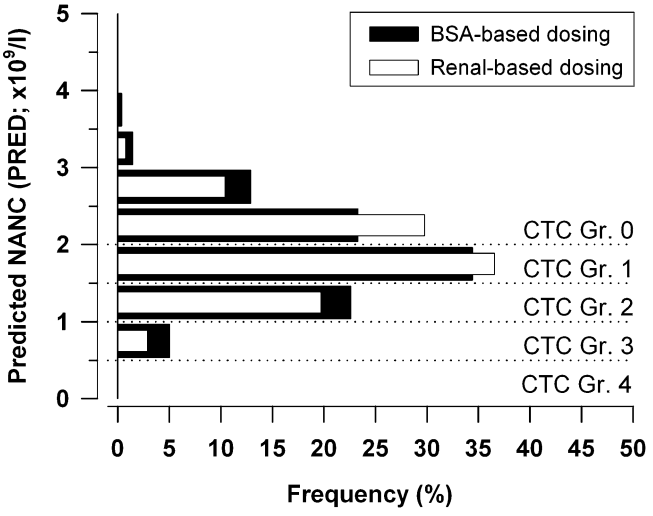

Fig. 5 Final population PK/PD model: comparison of NANC distributions for BSA-based and renal-based dosing for patients contained in the analysis dataset

Comparison of the variability in neutropenic response for BSA-based and renal function-based dosing

The distribution of model-predicted NANC values for a 500 mg/m^2 dose and renal function-based dosing, where dose was calculated to achieve an AUC of 163.7 μg·h/ml, is provided in Fig. 5. The figure illustrates that renal function-based dosing decreases the variability in NANC distribution relative to BSA-based dosing for the patient population represented in the analysis dataset, particularly at the tails of the distribution.

Time to nadir

The factors that most greatly influenced T_{Nadir} were AUC ($r^2 = 0.207$) and ALB ($r^2 = 0.236$). These results are consistent with ALB being included as a covariate for MTT and consistent with the impact of exposure on the timecourse of ANCs following pemetrexed administration. Predicted T_{Nadir} varied from approximately 8 to 9.6 days (192–230 h) as AUC varied from 38.3 μg·h/ml to 316 μg·h/ml and as ALB varied from 20.0 g/l to 49.0 g/l in the analysis population. The r^2 values for each of the remaining correlations between covariates contained in the final PK/PD model and T_{Nadir} were less than 0.05 (explained $<5\%$ of the variability).

Recovery time

Recovery time correlated with AUC ($r^2 = 0.247$ for $T_{Rec,0}$ versus AUC; $r^2 = 0.278$ for $T_{Rec,b}$ versus AUC; Fig. 6), which is consistent with the impact of exposure on the timecourse of ANCs following pemetrexed administration. Figure 6 presents predicted recovery times from time of drug administration. For patients

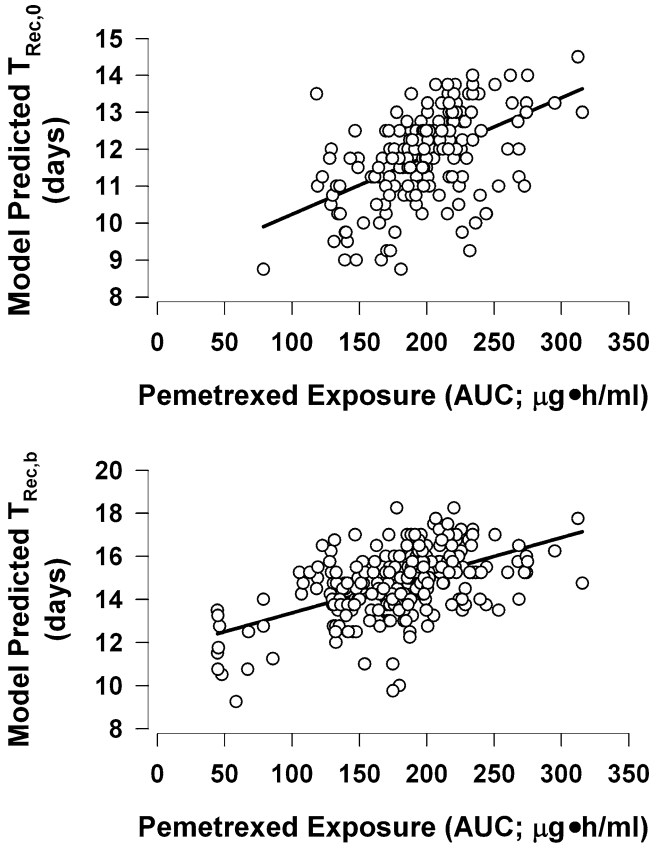

Fig. 6 Final population PK/PD model: individual estimates of recovery times from time of dose to CTC grade 0 neutropenia (*top panel*) and from time of dose to baseline absolute neutrophil count (*bottom panel*).
$T_{Rec,0}$ = time of recovery to CTC grade 0 neutropenia (i.e., ANC $>2\times10^9$/l). $T_{Rec,b}$ = time of recovery to baseline ANC

who became neutropenic (i.e., NANC $<2\times10^9$/l), the predicted recovery time to CTC grade 0 varied from approximately 9.9 to 13.6 days from the time of pemetrexed administration, which is from 1.6 to 3.9 days following the nadir. The predicted recovery time to cycle baseline ANC varied from approximately 12.3 to 17.2 days from the time of pemetrexed administration, which is from 4.24 to 7.49 days following the nadir. The r^2 values for each of the remaining correlations between covariates contained in the final PK/PD model and recovery times were less than 0.05 (explained $<5\%$ of the variability).

Discussion

An association between systemic drug exposure and a lowering of ANCs was identified during initial pemetrexed clinical development in an early phase I dose-escalation study [28]. In that study, the maximum tolerated dose of pemetrexed was 600 mg/m^2. However, an undesirable frequency of adverse events at the 600-mg/m^2 dose in subsequent phase II studies prompted a dose reduction to 500 mg/m^2. During that time, a classical multivariate statistical analysis was performed to identify potential factors that influenced pemetrexed toxicity [23]. Results from that analysis identified total HCY and/or methylmalonic acid concentrations (markers for folic acid and vitamin B_{12} deficiency) as significant predictors for patients to develop grade 3 and 4 toxicities, including severe neutropenia; HCY was predictive for severe neutropenia while methylmalonic acid was predictive for nonhematologic toxicities.

Friberg et al. [10] initially described a semimechanistic-physiologic PK/PD model characterizing chemotherapy-induced myelosuppression following administration of docetaxel, paclitaxel, etoposide, DMDC, CPT-11, or vinflunine. The PD portion of the model was characterized mathematically by three system-based parameters (MTT, BAS, and FP) that provide an adapted mathematical representation of the current understanding of underlying physiology, and a drug-effect parameter (DS) that relates the concentration of pemetrexed in plasma to the effect of the drug at the site of action. This model was used to analyse data that were collected from eight clinical studies evaluating pemetrexed as a single agent for the treatment of various cancer types [18].

Physiologically based models are generally more predictive than empirical models, with parameters that provide a mathematical characterization of the physiology of hematopoiesis [11]; therefore, they are preferred over the older empirical models. Although physiologically based models have superior predictive ability, the overall clinical impact of the various covariate effects and model parameters on ANC-time profile (eg, NANC, T_{Nadir}, and T_{Rec}) is not intuitively obvious. Therefore, simulations and correlation analyses were performed using the model to explore the effect of drug exposure (AUC) and the covariates included on PD model parameters on clinically relevant features of the ANC-time profile.

Drug exposure

Results from correlation and simulation analyses clearly demonstrated the impact of drug exposure on the NANC. All other covariates held constant, as AUC increased from 40 μg·h/ml to 300 μg·h/ml, NANC decreased from 4 (CTC grade 0) to 0.75 (CTC grade 3)$\times10^9$/l. When the impact on the NANC for each of the PD model covariates was evaluated with AUC held constant, a two to threefold lowering of NANC was found when each of the PD-associated covariates was varied over the ranges represented by the patient population evaluated in this analysis. Thus, both the pharmacokinetics of pemetrexed and patient-specific factors (covariates) associated with the PD model parameters affected the overall time course of neutropenia following drug exposure.

Analyses also confirmed the expected relationship of longer T_{Nadir} and longer T_{Rec} with increased exposure.

Because the population PK/PD approach allows a complete characterization of the entire ANC-time profile from a sparse sampling scheme, these analyses provided new insight regarding the specific timing of the NANC and the timecourse of recovery from neutropenic response. For patients who became neutropenic (i.e., NANC $< 2\times10^9$/l), the predicted recovery time to CTC grade 0 varied from approximately 9.9 to 13.6 days from the time of dose (1.6–3.9 days following the nadir). This finding, coupled with the lack of cumulative effect of pemetrexed exposure on NANC over multiple treatment cycles [18], suggests that a 14-day treatment cycle might be feasible for pemetrexed. As a practical matter, a 14-day treatment cycle would likely merit consideration only for single-agent pemetrexed administration. For combination therapy, it is unlikely that the dosing interval would be changed if the companion drug(s) is given on a 21-day treatment cycle. Additionally, these evaluations showed that recovery time to CTC grade 0 for patients treated with pemetrexed 600 mg/m^2 (“typical” AUC = 197 μg·h/ml) is only about 1 day longer than that for patients treated with pemetrexed 500 mg/m^2 (“typical” AUC = 164 μg·h/ml) (Fig. 6). This information may prove to be useful in further optimizing the dose and scheduling of pemetrexed.

Dose (500 mg/m^2 versus 600 mg/m^2)

Simulations using the population PK/PD model also compared the effect of pemetrexed starting doses of 500 mg/m^2 versus 600 mg/m^2 on the ANC-time profile and the frequency distribution of NANC values of a “typical” patient. The results indicated an increased probability of higher CTC grades of neutropenia at the higher dose. This result is consistent with clinical experience [28] and supports the programmatic decision to reduce the starting dose in all pemetrexed studies to 500 mg/m^2 in the absence of evidence that the higher dose provides a clinically relevant increase in efficacy. Studies to look for such evidence are ongoing.

Justification for vitamin supplementation

Niyikiza et al. [23] demonstrated that pretreatment vitamin deficiency marker status influenced the incidence and severity of neutropenia following single-agent administration in this patient population. Recent clinical experience has shown patients receiving folic acid and vitamin B_{12} supplementation prior to, and during, pemetrexed administration experience improved toxicity outcomes, including decreased hematologic toxicity without decreasing efficacy [22, 24, 30]. The simulations presented herein and the population PK/PD model results, which identified CYS and HCY as covariates with respect to the PD model parameters, presented in the preceding paper [18] further support the programmatic decision to introduce folic acid and vitamin B_{12} supplementation during pemetrexed clinical development to manage the risk of severe neutropenia secondary to pemetrexed administration.

Increased HCY and CYS, which are predictive of vitamin B_{12} and folate deficiency [1, 31] were shown to be associated with lower NANC. The probability that an otherwise “typical” patient would remain at CTC grade 0 toxicity decreased from approximately 50% to less than 20% for patients with elevated CYS and HCY. These results indicate that normalization of CYS and HCY levels with vitamin supplementation may lead to less severe neutropenia, and thus supports the present use of folic acid and vitamin B_{12} supplementation in pemetrexed-treated patients.

Dosing paradigm (BSA-based versus renal function-based dosing)

Renal function was the only factor that influenced pemetrexed CL [17, 21], and therefore, the only explanatory factor for systemic drug exposure for a given dose. Simulations have shown that systemic drug exposure is expected to have a greater influence on the ANC-time profile than any of the covariates. Because AUC is the strongest predictor of neutropenic response to pemetrexed administration, factors that affect pemetrexed exposure would naturally be expected to have an effect on the timecourse of neutropenia.

Consistent with the prevailing medical oncology-dosing paradigm, pemetrexed is dosed based on BSA. However, some drugs, such as carboplatin, are now dosed using AUC methods with more predictable and tolerable toxicity compared to the BSA-based methods [4]. Experts have increasingly challenged the indiscriminant use of BSA-based dosing [2, 6, 7, 9, 12, 13, 19, 20, 25–27, 29].

Since pemetrexed CL is related only to renal function [17, 21], for any given mg/m^2 dose, patients with diminished renal function would have increased pemetrexed exposure, and therefore an increased risk of developing neutropenia, than those who have normal renal function (creatinine clearance 90 ml/min). This suggests that dose adjustments based on renal function may offer additional control of hematologic response. Results from these analyses using simulations based on a semimechanistic-physiologic population PK/PD model also suggest that renal function-based dosing may provide decreased variability in patient response. This reduction in variability is a consequence of the lack of a PK basis for BSA-based dosing and the strength of impact of AUC on the timecourse of ANC following pemetrexed administration. BSA-based dosing actually introduces variability in the PD response for a constant BSA because of variability in CL (due to differing renal function), which results in differing exposures. Specifically, patients with low BSA coupled with high pemetrexed CL, and patients with high BSA coupled with low pemetrexed CL, could benefit from renal

function-based dosing relative to BSA-based dosing. While BSA-based dosing at 500 mg/m^2 as a single agent or in combination with other drugs is well tolerated for patients with creatinine clearance as low as 45 ml/min [8, 21], further studies evaluating renal function-based dosing should be undertaken to determine whether that dosing paradigm might afford more predictable efficacy and toxicity for individual patients.

Another important clinical issue asks the question: Can higher doses of pemetrexed be delivered when vitamin supplementation is included? A study to define the maximum tolerated dose of pemetrexed with vitamin supplementation is ongoing, and doses greater than 900 mg/m^2 have been achieved [14]. This may result in greater efficacy and acceptable toxicity at much higher doses of pemetrexed with supplementation compared to the maximum dose shown to be effective and safe without supplementation (i.e., 500 mg/m^2). However, additional studies are required to implement these higher doses in practice. As clinical development continues with higher pemetrexed doses and concomitant vitamin administration in an attempt to improve efficacy, our data suggest that a renal function-based dosing strategy may again merit consideration where it offers the potential to provide more predictable total systemic exposure, thereby ensuring that efficacy is maintained while controlling hematologic toxicity at doses that are nearer to the maximum tolerated dose.

While the current evaluation suggests only an incremental improvement in toxicity for renal function-based dosing over BSA-based dosing when all patients (CrCL from 33.3 to 225 ml/min) were considered, the improvement may be more significant for patients at the low end or below this range. This possibility needs to be tested further in future trials and can be further explored with simulation. Simulations examining NANCs for CrCL from 45 to 60 ml/min and incorporating both PK and PD variability will yield a more precise understanding of BSA-based versus renal function-based dosing specifically in that patient population.

In addition, the efficacy and safely of higher pemetrexed doses in combination with cisplatin or carboplatin needs to be studied. Since carboplatin is routinely dosed based on renal function to achieve a target AUC, the use of renal function-based dosing with higher doses of pemetrexed in this combination requires further testing.

In summary, this paper shows how information from correlation analyses and simulations using a semimechanistic-physiologic population PK/PD model for the characterization of neutropenia following pemetrexed administration may be helpful to quantify the impact of specific changes in dose and/or patient characteristics on NANC and T_{Rec}. The information gained from these evaluations provided supportive evidence for the decision to routinely include vitamin supplementation during pemetrexed treatment and provided information regarding the specific timing of the NANC and the timecourse of recovery for inclusion in product labeling. The results also suggest that a 14-day treatment cycle might be feasible for pemetrexed, which may further optimize the dose and scheduling of pemetrexed as a single agent. The clinical importance of identifying and making dosing adjustments for other covariates that affect the risk of severe neutropenia remains unclear and requires further investigation.

Pemetrexed is approved for first-line treatment of malignant pleural mesothelioma in combination with cisplatin and for second-line treatment of NSCLC as a single agent. The results presented herein are most relevant to single-agent therapy without vitamin supplementation. Further applications of these modeling and simulation approaches include: (1) dose optimization to support consideration of higher pemetrexed doses given in combination with vitamin supplementation, and (2) examining the impact of vitamin supplementation in minimizing toxicity while preserving efficacy in patients who have received pemetrexed in combination with other cytotoxic agents. The latter will require a modification of the model to account for the additional agent(s).

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