Population Pharmacokinetic/Pharmacodynamic Analyses of Pemetrexed and Neutropenia: Effect of Vitamin Supplementation and Differences between Japanese and Western Patients

Jane E. Latz, Karen Lee Schneck, Kazuhiko Nakagawa, Mary Alice Miller, and Chris H. Takimoto

Abstract

Purpose: The objectives of the analysis were to characterize the time course of neutropenia after pemetrexed administration using an established semimechanistic-physiologic model, characterize the relationship between pemetrexed exposure and neutropenia, and describe differences in neutropenic response by vitamin supplementation status and between Japanese and Western patients.

Experimental Design: An eight-compartment population pharmacokinetic/pharmacodynamic model was used to describe the absolute neutrophil count (ANC) -time profile (neutropenic response) following pemetrexed doses of 300 to 1,400 mg/m² administered every 21 days. The analyses pooled data from 13 studies including 279 patients (161 supplemented with oral folic acid and intramuscular vitamin B₁₂, and 118 unsupplemented; 248 Western and 31 Japanese) who received 857 treatment cycles.

Results: Vitamin supplementation status, ethnic origin, and drug exposure were the dominant predictors of neutropenic response. Vitamin supplementation diminishes neutropenic response to pemetrexed. Model-predicted ANC nadirs for the “typical” Western patient receiving 500 mg/m² pemetrexed ± vitamin supplementation were 2.74 × 10⁹/L and 1.70 × 10⁹/L, respectively. Japanese patients had a less pronounced neutropenic response to pemetrexed relative to Western patients. The model-predicted ANC nadir for Japanese patients receiving 500 mg/m² pemetrexed with vitamin supplementation was 2.66 × 10⁹/L. Values for the 1,000 mg/m² dose with vitamin supplementation were 1.91 × 10⁹/L and 1.34 × 10⁹/L for Japanese and Western patients, respectively. Increased albumin, decreased cystathionine, and decreased body surface area were also associated with increased neutropenic response.

Conclusions: The neutropenic response to higher pemetrexed doses administered with vitamin supplementation is tolerable. All other factors equal, Japanese patients have a lesser neutropenic response to pemetrexed relative to Western patients.

Pemetrexed (Alimta) is a novel anticancer agent that has been approved in combination with cisplatin for the treatment of patients with malignant pleural mesothelioma (1) and as single-agent therapy for second-line treatment of non-small cell lung cancer (2). It has also recently been approved in combination with cisplatin as first-line treatment of non-small cell lung cancer (3). In addition to mesothelioma and non-small cell lung cancer, pemetrexed has shown clinical activity and is being evaluated in a variety of tumor types (4–14). The recommended dose of pemetrexed is 500 mg/m² administered as a 10-min intravenous infusion on day 1 of a 21-day cycle.

Pemetrexed acts primarily by inhibiting thymidylate synthase (15, 16), thereby decreasing the amount of thymidine available for DNA synthesis. Pemetrexed also inhibits dihydrofolate reductase and glycaminamide ribonucleotide formyl transferase, a folate-dependent enzyme that is involved in purine synthesis (16). The principal toxicity observed following single-agent administration of pemetrexed is common toxicity criteria (CTC) grade 3 or 4 neutropenia (14). Because patients with elevated baseline homocysteine levels have a higher risk of developing severe toxicity during treatment (17), patients in pemetrexed clinical studies routinely receive concomitant folic acid (350-1,000 µg/d) and vitamin B₁₂ (1,000 µg intramuscularly every 9 weeks) supplementation (17).

Semimechanistic-physiologic population pharmacokinetic/pharmacodynamic modeling is a technique that has been used to describe myelosuppression following administration of a cytotoxic agent (18, 19). The model was used previously to analyze data from eight cancer trials in which patients received pemetrexed, 500 or 600 mg/m² without vitamin...
supplementation, to examine neutropenic response [absolute neutrophil count (ANC) versus time, including the time course, severity (nadir depth), and recovery time of ANC] after single-agent pemetrexed administration and to identify patient characteristics associated with variability in neutropenic response (20, 21). These previous population pharmacokinetic/pharmacodynamic analyses identified factors affecting the severity and time course of neutropenia following pemetrexed administered without vitamin supplementation to Western patients (predominantly Caucasian).

The current analyses applied the same analytic approach as that in the previous population pharmacokinetic/pharmacodynamic analyses (20, 21) but incorporated data from five additional studies in Western and Japanese patients, the majority (>90%) of whom received pemetrexed with vitamin supplementation. Specific objectives were to (a) characterize the time course of neutropenia in Japanese and Western patients after pemetrexed administration using an established semimechanistic-physiologic model, (b) characterize the relationship between pemetrexed systemic exposure and neutropenia in these patients, and (c) describe differences in neutropenic response by vitamin supplementation status and between Japanese and Western patients.

**Clinical and Methods**

**Clinical studies and data collection.** The analyses included data from 279 patients, with various tumor types, enrolled in 13 single-agent pemetrexed studies. Seven of the eight phase II studies included in the original analyses enrolled only chemonaive patients; the remaining study and the additional studies incorporated in the current analyses included patients who received prior chemotherapy and/or radiation therapy (radiation treatments were to have been completed at least 3 weeks before study entry and chemotherapy at least 2 weeks before study entry). Patients were to have recovered from any acute toxicities associated with prior therapy. The analyses included data from 118 patients who did not receive vitamin supplementation and 161 patients who received oral folic acid and intramuscular vitamin B12 supplementation.

The primary objectives for the studies that were pooled for these analyses included the determination of response rate in individual tumor types for patients treated with pemetrexed, determination of maximum tolerated dose with vitamin supplementation, evaluation of pemetrexed tolerability and pharmacokinetics in patients with varying degrees of renal function, and assessment of potential drug-drug interactions.

Eligibility criteria included male and nonpregnant, nonlactating female patients at least 18 years old, histologically or cytologically confirmed carcinoma, an estimated life expectancy of at least 12 weeks, and a performance status of 0 to 2 as per the Eastern Cooperative Oncology Group scale. The trials were approved by the relevant ethics committee at the participating medical institutions. All participants gave written informed consent before study enrollment, and studies were conducted according to the ethical principles of the most recent version of the Declaration of Helsinki.

Patient dosing was based on body surface area (BSA) and patients were initially assigned to receive pemetrexed, 300 to 1,400 mg/m², as a 10-min intravenous infusion every 21 days. Dose adjustments (reductions) at the start of subsequent courses of therapy were based on nadir counts or maximal nonhematologic toxicity from the preceding cycle. The American Society of Clinical Oncology guidelines for the use of colony-stimulating factors were to be followed for patients with grade 4 neutropenia, neutropenic fever, or documented infections during neutropenic episodes. Routine prophylactic use of colony-stimulating factors was not permitted during the studies. Prophylactic use of dexamethasone (4 mg twice a day on the day before, the day of, and the day after each dose of pemetrexed) to treat rash was allowed in each of the studies, except for the phase I study conducted in Japanese patients (31 patients).

Pemetrexed concentration determinations, hematology, blood chemistry, and measurement of vitamin deficiency markers were done at central laboratories with common methodology and quality control. Both sparse and intensive pharmacokinetic sampling schemes were used in these studies. Samples for measurement of pemetrexed concentration were collected for up to 36 to 48 h after dose administration during cycle 1 of each study and also during cycle 2 or 3 of most of the studies.

Blood samples for determination of neutrophil counts were collected at the start of each new cycle (before receiving pemetrexed) and approximately weekly thereafter. Blood chemistry evaluations were done on samples collected at the start of each cycle and 1 week after receiving pemetrexed. Vitamin deficiency marker concentrations (homocysteine, cystathionine, methylmalonic acid, and methylcitrates I and II) were measured in samples collected at the start of each new cycle. Additional patient parameters [e.g., BSA and estimated creatinine clearance (CrCl)] were derived using standard formulas (22, 23).

**Data assembly and pharmacokinetic/pharmacodynamic modeling approach.** Pharmacokinetic and pharmacokinetic/pharmacodynamic analyses were conducted using the nonlinear mixed-effect modeling program version V using a two-stage (sequential) approach. Pharmacokinetic parameters incorporated into the data set used for population pharmacokinetic/pharmacodynamic analysis were estimated using a three-compartment pharmacokinetic model that incorporated renal function and BSA (24). Post hoc estimates of CL, central volume distribution (V1), peripheral volumes of distribution (V2 and V3), and intercompartmental CL (Q2 and Q3) for individual treatment cycles were incorporated into the pharmacokinetic/pharmacodynamic data set. ANC data were combined with dosing information, patient demographics (age and gender) and characteristics (BSA and weight), clinical laboratory results (blood chemistry and vitamin deficiency markers), and pharmacokinetic parameter estimates to produce the data set used for population pharmacokinetic/pharmacodynamic analysis. When available, the pharmacokinetic/pharmacodynamic data set...
incorporated individual empirical Bayesian estimates of pharmacokinetic parameters; otherwise, population estimates based on the population pharmacokinetic model were used for patients with missing plasma concentration-time data. All ANC data for a given patient were modeled simultaneously using the nonlinear mixed-effect modeling subroutine ADVAN6.

A semimechanistic-physiologic population pharmacokinetic/pharmacodynamic model was used to characterize the time course of neutrophil counts following single-agent pemetrexed administration. The pharmacodynamic portion of the model, described in detail previously (20), was constructed to mimic physiologic processes and consists of five compartments that mimic the maturation of progenitor cells in bone marrow to circulating neutrophils: a stem/progenitor cell compartment, three maturation compartments, and a circulation compartment (Fig. 1). The combined pharmacokinetic/pharmacodynamic model therefore comprised a total of eight compartments: three compartments governing the pharmacokinetic portion of the model and five compartments governing the pharmacodynamic portion of the model.

Because earlier results showed that vitamin metabolite levels are important covariates, model development was done using only treatment cycles for which vitamin metabolite data were available. Other patient characteristic data that were evaluated as potential covariates were systematically imputed onto subsequent records of the nonlinear mixed-effect modeling data set to replace missing values.

Only patient data that were evaluated as covariates were carried forward to replace missing values. Response data (ANC) were not carried forward. Because modeling incorporated only data from those cycles for which actual ANC results were available and previous analyses have shown that the parameter estimates were consistent across treatment cycles (no time-dependent bias in parameter estimates and therefore no bias due to dropouts; ref. 20), a correction for dropout was not incorporated into the model.

Model development. The established semimechanistic-physiologic structural model (20, 21) was fit to the ANC time data without covariates. Four structural pharmacodynamic parameters were estimated: baseline ANC (BAS), mean transit time (MTT) that quantifies the maturation time of a committed stem progenitor cell to a mature circulating neutrophil, dose stimulus variable (DS) that quantifies the effect of systemic pemetrexed exposure, and a feedback parameter (FP) that quantifies the strength of the feedback action resulting from release of endogenous colony-stimulating factors. Between-patient variability models assumed a log-normal distribution (a proportional error structure) of individual BAS, MTT, DS, and FP values. Both proportional and combined additive/proportional residual error models were evaluated. Consistent with previous analyses, the first-order method was employed throughout the current analyses. The comparison of two nested models was based on the change in the minimum objective function value (ΔMOF), the agreement between predicted and observed values, the magnitude and randomness of residual values as assessed by visual inspection, and the precision of estimates.

In the semimechanistic-physiologic model that is the subject of this report, the BAS, MTT, and FP are all system-based (providing a mathematical representation of the current understanding of the underlying physiology), whereas the DS is a drug-related. As described previously (20, 21), patient-specific factors that affect either the system-based parameters or the drug-related in this model result in changes to the ANC-time profile. Thus, patient-specific factors were evaluated as covariates with respect to each of the four model parameters. Patient factors considered as potential covariates in the current analyses were limited to (a) those identified as covariates previously (homocysteine, cystathionine, serum albumin, serum total protein, and BSA), (b) vitamin metabolites not identified previously as covariates (methim proximal lonic acid and methylcitrates I, II, and total), and (c) vitamin supplementation status and origin (Western versus Japanese).

A full model was developed using established covariate search and model development strategies (20, 21). Potential covariates were added to the model sequentially based on the change in the MOF for the individual covariate; those covariates that reduced the objective function the most were added to the model first. Potential covariates that did not result in a decrease in the MOF ≥ 3.841 (P < 0.05) on sequential addition to the model were removed from the analysis. Once a full model was established, the process was then reversed, with each potential covariate removed individually from the full model. Covariates were retained in the final model if they resulted in a statistically significant increase in MOF (≥ 10.828 points for 1 df; P < 0.001) when removed from the full model.

Objective function mapping and leverage analysis were used to evaluate the robustness of the population pharmacokinetic/pharmacodynamic model as described previously (20, 21).

The effects of pemetrexed exposure, vitamin supplementation status, and origin relative to ANC nadir for subpopulations of interest (unsupplemented Western patients, supplemented Western patients, and supplemented Japanese patients) were examined graphically using model-predicted nadirs from complete model-predicted ANC-time profiles for each of the patients included in the analysis. The final pharmacokinetic/pharmacodynamic model was used to generate the ANC-time profiles, with ANC predicted at 6-h intervals throughout the evaluation period as described previously (21).

Results

Patient characteristics and dose administration. Population pharmacokinetic/pharmacodynamic evaluations included 279 patients (from eight phase II and five phase I studies), ages 25 to 80 years, who received a total of 857 treatment cycles. The Western (88.9%) patients were predominantly Caucasian (199 of 248), and there were slightly more male (56% overall) than female patients (Table 1). ANC data included 307 cycles without vitamin supplementation administered to Western patients, 427 cycles with vitamin supplementation to Western patients, and 123 cycles with vitamin supplementation to Japanese patients.

Initial pemetrexed doses for patients included in these analyses ranged from 300 to 1,410 mg/m². The overall range of actual doses administered was 74.9 to 1,410 mg/m². Absolute (nonnormalized) total doses ranged from 126 to

![Fig. 1. Neutrophil cell proliferation model with feedback. The combined pharmacokinetic/pharmacodynamic model is composed of eight total compartments: three governing the pharmacokinetic portion and five governing the pharmacodynamic portion of the model. The five pharmacodynamic compartments mimic the maturation of progenitor cells in bone marrow to circulating neutrophils: a stem/progenitor cell compartment, three maturation compartments, and a circulation compartment.](image-url)
2,740 mg and corresponded to overall exposures, expressed as areas under the concentration curve (AUC), ranging from 37.4 to 612 g/h/mL.

**Population pharmacokinetic model.** A three-compartment population pharmacokinetic model, incorporating CrCl as a covariate relative to CL and BSA as a covariate relative to V1, V2, and V3, was used to characterize the pharmacokinetics of pemetrexed in this patient population and to estimate pharmacokinetic parameters that were then incorporated into the pharmacokinetic/pharmacodynamic analysis. The model is summarized as follows:

\[
\begin{align*}
CL &= 163 \times \frac{CrCl}{(82.1 + CrCl)} \\
Q2 &= 1.13 \\
Q3 &= 137 \\
V1 &= 7.00 \times \frac{BSA}{1.81} \wedge 1.12 \\
V2 &= 1.69 \\
V3 &= 7.87 \times \frac{BSA}{1.81} \wedge 1.24
\end{align*}
\]

Between-patient variabilities for CL, V1, and V3 were 21.4%, 24.4%, and 27.5%, respectively. Residual error was 27.0%. There were no differences in pemetrexed pharmacokinetics based on vitamin supplementation status and no differences in pemetrexed pharmacokinetics between Western and Japanese patients.

**Population pharmacokinetic/pharmacodynamic model.** The population pharmacokinetic/pharmacodynamic model is summarized in Table 2. The model includes vitamin supplementation status, origin, cystathionine, albumin, and BSA as covariates relative to the pharmacodynamic model parameters, with vitamin supplementation status and origin identified as covariates relative to more than one model parameter.

Diagnostic plots showed good agreement between predicted and observed neutrophil counts as well as by weighted residual values (data not shown). Objective function mapping for the base values of BAS, MTT, DS, FP, each of the covariate parameter, and variability terms indicated that the parameter were estimated with good precision. Leverage analysis did not identify significant differences when subsets of patient data were systematically removed from the analysis data set. All parameter estimates from the leverage analyses were within the 95% confidence interval obtained from objective function mapping. Thus, both objective function mapping and leverage analysis showed the model parameter to be well estimated, thereby supporting the validity of the model to describe the time course of ANC after pemetrexed administration in this patient population (data not shown).

**Covariate effects relative to neutropenic response and the ANC-time profile.** As indicated above, the model included vitamin supplementation status, origin, cystathionine, albumin, and BSA as covariates relative to the pharmacodynamic model parameter. The model parameter, the covariates, and the effect of varying the model parameter and covariates on the clinically relevant features of the ANC-time profile (ANC nadir, timing of ANC nadir, and recovery time) are summarized in Table 3. Systemic drug exposure, vitamin supplementation status, and origin were identified as dominant predictors of neutropenic response in these analyses and each of the effects is examined individually below.

The effect of pemetrexed exposure on neutropenic response is illustrated in Fig. 2A and B. Each panel compares the ANC-time profiles following 500 and 1,000 mg/m² pemetrexed doses administered with vitamin supplementation for a "typical" (central tendency) Western patient (Fig. 2A) and for a "typical" Japanese patient (Fig. 2B). The lower ANC nadir associated with the 1,000 mg/m² dose relative to the 500 mg/m² dose (a doubling of the exposure) was more pronounced for Western patients than for Japanese patients.

Because all patients in the Japanese study received pemetrexed with vitamin supplementation, the effect of vitamin supplementation on neutropenic response is illustrated for Western patients only (Fig. 2C). Strong relationships between vitamin supplementation status and DS (ΔMOF = 93.061; P < 0.001), and vitamin supplementation status and MTT (ΔMOF = 34.775; P < 0.001) were identified. The combined effects of the decreases in MTT and DS on the ANC-time profile resulting from vitamin supplementation are illustrated in Fig. 2C. Patients receiving the same dose of pemetrexed without vitamin supplementation have lower ANC nadirs and longer recovery times compared with patients receiving pemetrexed with vitamin supplementation.

Strong associations between origin and BAS (ΔMOF = 45.444; P < 0.001), origin and DS (ΔMOF = 64.060; P < 0.001), and origin and FP (ΔMOF = 18.515; P < 0.001) were identified. The combined effect of these relationships on the ANC-time profile is illustrated in Fig. 2D and E. Although the decrease in DS for Japanese patients lessens the magnitude of neutropenia, this effect is counteracted by the lower BAS for Japanese patients such that (all other factors being equal) there

### Table 1. Baseline patient characteristics (n = 279)

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td><strong>Male</strong></td>
</tr>
<tr>
<td>Female</td>
<td>122 (43.7)</td>
</tr>
<tr>
<td>Male</td>
<td>157 (56.3)</td>
</tr>
<tr>
<td><strong>Origin</strong></td>
<td><strong>Western</strong></td>
</tr>
<tr>
<td>Japanese</td>
<td>248 (88.9)</td>
</tr>
<tr>
<td>Japanese</td>
<td>31 (11.1)</td>
</tr>
<tr>
<td><strong>Vitamin supplementation</strong></td>
<td><strong>Not supplemented</strong></td>
</tr>
<tr>
<td><strong>Supplemented</strong></td>
<td>161 (57.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Mean (CV%, range)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight, kg</strong></td>
<td>72.5 (32.8, 32.7-127)</td>
</tr>
<tr>
<td><strong>BSA, m²</strong></td>
<td>1.82 (1.24-2.60)</td>
</tr>
<tr>
<td><strong>CrCl, mL/min</strong></td>
<td>99.5 (34.8, 16.2-335)</td>
</tr>
<tr>
<td><strong>Total protein, g/L</strong></td>
<td>70.5 (56.0-93.0)</td>
</tr>
<tr>
<td><strong>Albumin, g/L</strong></td>
<td>35.3 (20.0-49.0)</td>
</tr>
<tr>
<td><strong>Cystathionine, nmol/L</strong></td>
<td>303 (68.7, 66.0-1620)</td>
</tr>
<tr>
<td><strong>Homocysteine, μmol/L</strong></td>
<td>8.54 (7.0-28.1)</td>
</tr>
<tr>
<td><strong>Methycitrivite I, nmol/L</strong></td>
<td>56.6 (48.5, 11.0-217)</td>
</tr>
<tr>
<td><strong>Methycitrivite II, nmol/L</strong></td>
<td>80.4 (47.5, 16.0-301)</td>
</tr>
<tr>
<td><strong>Total methycitrivite, nmol/L</strong></td>
<td>137 (44.8, 28.0-454)</td>
</tr>
<tr>
<td><strong>Methyilmalonic acid, nmol/L</strong></td>
<td>175 (57.4, 35.0-1150)</td>
</tr>
</tbody>
</table>

**Abbreviation:** NR, normal range.

*Estimated using the original weight-based Cockcroft-Gault formula.
is little difference in ANC nadir for Japanese patients relative to Western patients for the 500 mg/m² dose (Fig. 2D). For the 1,000 mg/m² dose, however, the effect of decreased DS for Japanese patients was more evident because the ANC nadir for Western patients was lower than that for Japanese patients despite the higher BAS for Western patients (Fig. 2E). The relationship between origin and FP is reflected in an increased recovery time for Japanese patients relative to Western patients.

Although albumin, cystathionine, and BSA were identified as significant covariates (Table 2), the magnitude of each of these effects was less than that for vitamin supplementation, origin, or exposure. Therefore, the effects for albumin, cystathionine, and BSA are of lesser clinical interest.

Table 3 integrates the effects of pemetrexed exposure, vitamin supplementation status, and origin relative to ANC nadir for each of the three subpopulations of interest: unsupplemented Western patients (Fig. 3A), supplemented Western patients (Fig. 3B), and supplemented Japanese patients (Fig. 3C). Because pemetrexed exposure is a reflection of CL and therefore renal function (GFR), renal function is also shown in these plots. The results illustrate that patients who received pemetrexed without vitamin supplementation have a higher likelihood of developing neutropenia that is one to two

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population estimate (%SEE)*</th>
<th>Between-patient variability (%SEE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAS</td>
<td>9.29 (9.76)</td>
<td>33.4% (13.2)</td>
</tr>
<tr>
<td>TVMTT</td>
<td>102 (3.25)</td>
<td>19.5% (35.7)</td>
</tr>
<tr>
<td>TVDS</td>
<td>0.222 (7.16)</td>
<td>51.0% (19.2)</td>
</tr>
<tr>
<td>TVFP</td>
<td>0.152 (7.30)</td>
<td>32.8% (34.4)</td>
</tr>
<tr>
<td>Residual error (additive)</td>
<td>0.725 (20.7)</td>
<td></td>
</tr>
<tr>
<td>Residual error (proportional)</td>
<td>31.3% (14.9)</td>
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</table>

*Estimation method: first order.

### Abbreviations
- ALB: albumin
- CYS: cystathionine
- ETH: indicator for Japanese
- FP: FP that quantifies the strength of the feedback action from the colony-stimulating factors
- MTT: MTT of a progenitor cell to a mature neutrophil
- VS: indicator for vitamin supplementation
- SEE: SE of the estimate
- BASINT is the intercept term (ALB = 0 and CYS = 303)
- TVDS, TVFP, and TVMTT are "typical values" for each of the parameters

### Population Pharmacokinetic/Pharmacodynamic Model

#### Unsupplemented Western Patients
- \(\text{BAS} = \text{BASINT}(1 + (\text{ALB}/35.3) \times k_1) \times (\text{CYS}/303)^{k_2}\)
- \(\text{MTT} = \text{TVMTT}\)
- \(\text{DS} = \text{TVDS} + (\text{BSA} - 1.83) \times k_5\)
- \(\text{FP} = \text{TVFP}\)

#### Supplemented Western Patients
- \(\text{BAS} = \text{BASINT}(1 + (\text{ALB}/35.3) \times k_1) \times (\text{CYS}/303)^{k_2}\)
- \(\text{MTT} = \text{TVMTT}\)
- \(\text{DS} = \text{TVDS} + (\text{BSA} - 1.83) \times k_5\)
- \(\text{FP} = \text{TVFP}\)

### Japanese Patients
- \(\text{BAS} = \text{BASINT}(1 + (\text{ALB}/35.3) \times k_1) \times (\text{CYS}/303)^{k_2}\)
- \(\text{MTT} = \text{TVMTT}\)
- \(\text{DS} = \text{TVDS} + (\text{BSA} - 1.83) \times k_5\)
- \(\text{FP} = \text{TVFP}\)

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</tr>
<tr>
<td>(k_1)</td>
<td>-0.360 (17.2)</td>
<td></td>
</tr>
<tr>
<td>(k_2)</td>
<td>0.117 (26.4)</td>
<td></td>
</tr>
<tr>
<td>(k_3)</td>
<td>0.691 (10.8)</td>
<td></td>
</tr>
<tr>
<td>TVMTT</td>
<td>102 (3.25)</td>
<td>19.5% (35.7)</td>
</tr>
<tr>
<td>(k_4)</td>
<td>0.887 (4.89)</td>
<td></td>
</tr>
<tr>
<td>TVDS</td>
<td>0.222 (7.16)</td>
<td>51.0% (19.2)</td>
</tr>
<tr>
<td>(k_5)</td>
<td>-0.144 (28.8)</td>
<td></td>
</tr>
<tr>
<td>(k_6)</td>
<td>0.333 (29.7)</td>
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### Table 3.

<table>
<thead>
<tr>
<th>Model variable</th>
<th>Effect on ANC-time profile</th>
<th>Covariate</th>
<th>Effect of covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAS</td>
<td>(\text{BAS} \Rightarrow \text{ANCn})</td>
<td>Origin</td>
<td>Origin = Western (\Rightarrow)</td>
</tr>
<tr>
<td>CYS</td>
<td>(\text{CYS} \Rightarrow \text{ANCn})</td>
<td>ALB</td>
<td>ALB (\Rightarrow)</td>
</tr>
<tr>
<td>ALB</td>
<td>(\text{ALB} \Rightarrow \text{ANCn})</td>
<td>VS</td>
<td>VS (=) supplemented (\Rightarrow)</td>
</tr>
<tr>
<td>DS</td>
<td>(\text{DS} \Rightarrow \text{ANCn} = \text{ANC}<em>{\text{Nadir}} = \text{ANC}</em>{\text{Trec}})</td>
<td>Origin</td>
<td>Origin = Japanese (\Rightarrow)</td>
</tr>
<tr>
<td>BSA</td>
<td>(\text{BSA} \Rightarrow \text{ANCn} = \text{ANC}_{\text{Trec}})</td>
<td>BSA</td>
<td>BSA (\Rightarrow)</td>
</tr>
<tr>
<td>FP</td>
<td>(\text{FP} \Rightarrow \text{ANC}_{\text{Trec}})</td>
<td>Origin</td>
<td>Origin = Western (\Rightarrow)</td>
</tr>
<tr>
<td>AUC</td>
<td>(\text{AUC} \Rightarrow \text{ANCn})</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Estimation method: first order.

### Abbreviations
- ANCn: absolute neutrophil count nadir
- DS: dose-stimulus parameter
- TVMTT: time from dose administration to occurrence of ANC nadir
- TVFP: time from dose administration to recovery from neutropenic response
- VS: vitamin supplementation
- N/A: not applicable
CTC grades more severe than patients who received pemetrexed with vitamin supplementation (Fig. 3D). The effect of declining renal function on the ANC nadir for each subpopulation is shown in each of the panels via the corresponding increase in AUC.

**Discussion**

Current clinical practice requires the use of vitamin B₁₂ and oral folic acid or multivitamin cotherapy to reduce the toxic effects of pemetrexed. This dosing strategy was implemented based on findings from a multivariate analysis that showed a correlation between a high homocysteine and/or methylmalonic acid plasma concentrations and an increased incidence of CTC grade 3 and 4 toxicities (17). Neutropenia was one of the most pronounced hematologic toxicities observed.

Previous population pharmacokinetic/pharmacodynamic analyses characterized the time course of neutropenic response following pemetrexed administered without vitamin supplementation (20, 21). The current analyses, which built on prior analyses, incorporated data from patients who received vitamin cotherapy, thus enabling additional quantitation and mechanistic characterization of the effect of vitamin supplementation on the severity of pemetrexed hematologic toxicity. The covariates from the previous model were evaluated in the current analyses. In addition, vitamin metabolites that did not meet the criteria for inclusion in the previous model were again evaluated as potential covariates in the current analyses. Finally, the inclusion of more recently available data from the Japanese dose-finding study and from patients who received pemetrexed with vitamin supplementation enabled the evaluation of vitamin supplementation status and origin [Western (predominantly Caucasian) versus Japanese patients] as covariates. Covariate effects in the final model identified in these analyses included origin, albumin, and cystathionine relative to BAS; vitamin supplementation status relative to MTT; vitamin supplementation status, origin, and BSA relative to DS; and origin relative to FP (Table 2).

The earlier model, based on data for patients who did not receive vitamin supplementation, included cystathionine, homocysteine, albumin, total protein, and BSA as covariates (20, 21). Although the current model also included cystathionine, albumin, and BSA as covariates, it did not include homocysteine or total protein. Albumin, which was identified as a covariate with respect to BAS in the current analyses, was previously a covariate with respect to MTT. The relationships between cystathionine and BAS (lower cystathionine corresponding to lower ANC nadir) and between BSA and DS (lower BSA corresponding to lower ANC nadir) in the current model are consistent with those identified previously (21).

There are several explanations for why vitamin supplementation was retained as a covariate in the current model instead
of homocysteine, which was a covariate in the previous model. The vitamin supplementation covariate in the current model essentially incorporates the informative value of the homocysteine covariate from the previous model. Although the two covariates affect different parameter in the two models, the overall effect on the neutropenic response is similar. The inclusion of vitamin supplementation status (a categorical covariate), despite a normal distribution of homocysteine values across the combined data set encompassing both patients who received vitamin supplementation and those who did not, may reflect additional beneficial effects of vitamin supplementation beyond those attributable to reductions in homocysteine level alone. Although the current model is slightly different than that described previously, the neutropenic response predicted for the “typical” Western patient (“central tendency”) receiving 500 mg/m² without vitamin supplementation was similar to that predicted by the previous model.

Vitamin supplementation status and origin were identified as covariates with respect to multiple model parameter: both the system-based parameter and the drug-related parameter (DS). The predominant effect for both of these covariates was observed with the DS parameter (the only drug-related parameter). Vitamin supplementation and Japanese origin were both associated with a decrease in DS and therefore a decrease in the severity of the neutropenic response. The inclusion of vitamin supplementation status and origin as covariates with respect to DS indicates that they directly affect the neutropenic response to pemetrexed.

Although it is not immediately evident why the neutropenic response to pemetrexed in Japanese patients was less pronounced than that in Western patients, it is possible that the difference between the subpopulations in DS may be due to a more folate-rich diet in Japanese patients (25, 26). Lower cystathionine and homocysteine levels for vitamin-supplemented Japanese patients relative to vitamin-supplemented Western patients are consistent with this possibility. A difference between populations in toxicity based on origin is also consistent with the results of a study that documented differences between Western and Japanese patients in the toxicity profiles of uracil/tegafur/leucovorin (27), but despite these differences the uracil/tegafur/leucovorin combination was equally effective in the two populations.

The identification of vitamin supplementation and origin as covariates relative to system-based parameter suggests that, in addition to affecting the drug-related aspect of the neutropenic response, they also affect the neutropenic response via the underlying physiology. Specifically, vitamin supplementation appears to decrease MTT, which shortens the recovery time from neutropenia. The identification of vitamin supplementation as a covariate with respect to MTT in the current analyses suggests that vitamin supplementation may exert a general effect and therefore may potentially ameliorate neutropenic response following administration of cytotoxic agents other than antifolates. The previous analyses identified homocysteine and cystathionine (vitamin metabolite markers of folate status) as covariates with respect to system-based parameter, suggesting that vitamin supplementation may exert a drug-independent effect (20).

In these studies, Japanese origin was associated with a lower BAS, which corresponds to a lower ANC nadir. It is
questionable, however, whether the difference between Western and Japanese patients in BAS is actually related to differences in physiology or whether the difference may be a reflection of standards of medical practice and/or concurrent medications. Each of the studies included in these analyses, except the Japanese study, allowed prophylactic use of dexamethasone, a synthetic glucocorticoid, to treat rash. Glucocorticoids are known to increase WBC counts (28).

These analyses also showed the magnitude of the effect of pemetrexed pharmacokinetics (total systemic exposure) on the ANC-time profiles. Increases in systemic exposure (AUC) are expected to increase the potential for a patient to develop more severe neutropenia. Thus, any factors that affect pemetrexed exposure would also be expected to have an effect on the time course of neutropenia. Because population pharmacokinetic analyses have clearly shown that renal function is the only explanatory parameter with respect to drug CL, patients with diminished renal function would have a greater probability of developing more significant neutropenia than those with normal renal function for any given dose based on BSA. For Japanese patients receiving pemetrexed, 1,000 mg/m², the “typical” patient with normal renal function (CrCL of 90 mL/min) will have an ANC nadir of 1.90 × 10⁹/L (CTC grade 1), and the patient with diminished renal function (CrCL of 45 mL/min) will have an ANC nadir of 1.39 × 10⁹/L (CTC grade 2). This suggests that neutropenia and toxicities with the 1,000 mg/m² dose would be manageable even for patients with impaired renal function.

The currently established pemetrexed dose (500 mg/m²) was determined without vitamin supplementation (29). The phase I dose-escalation studies of single-agent pemetrexed with vitamin supplementation in patients with solid tumors (24, 30) showed that higher doses of pemetrexed could be administered without intolerable toxicities. These analyses characterized the effect of high versus low doses on neutropenic response and provided additional quantitative evidence for the tolerability of higher doses. Results from two recently completed randomized studies showed that higher doses of single-agent pemetrexed confirmed that toxicity remained manageable for higher pemetrexed doses administered with vitamin supplementation. One of these studies, a phase III study for second-line treatment of patients with non-small cell lung cancer that enrolled predominantly Western patients, showed a slightly higher, but manageable, toxicity in the high-dose treatment arm (900 mg/m²) relative to the standard dose (31). The other, a phase II study of pemetrexed for second-line treatment of Japanese patients with non-small cell lung cancer also showed manageable toxicity for the high-dose treatment arm (1,000 mg/m²) relative to the standard dose (32). The studies evaluating higher doses of single-agent pemetrexed did not, however, show an efficacy advantage for higher doses relative to the established 500 mg/m² dose.

These analyses highlight a novel model-based strategy for understanding the differences in pharmacodynamic outcomes between patient populations and quantifying those differences in a systematic fashion. This approach improves our understanding of the variability in clinical outcome resulting from pharmacokinetic and pharmacodynamic variability and provides insights for modulating drug toxicity for future clinical trials. The semimechanistic-physiologic population model, which provides an opportunity to simulate clinical scenarios, is a valuable method for understanding how alterations in dose, differences in systemic exposure due to factors effecting pharmacokinetic variability, and vitamin supplementation affect the tolerability of pemetrexed in various populations.

In summary, the time course of the neutropenic response after pemetrexed administration was characterized based on data available from 857 treatment cycles administered to 279 patients participating in phase I and II pemetrexed studies. The neutropenic response observed with 1,000 mg/m² pemetrexed with vitamin supplementation is similar in magnitude relative to that observed with 500 mg/m² without vitamin supplementation. These analyses also show that, all other factors being equal, Japanese patients have a less pronounced neutropenic response to pemetrexed than do Western patients.

Disclosure of Potential Conflicts of Interest

J.E. Latz, K.L. Schneck, and M.A. Miller are employed by and have an ownership interest in Eli Lilly and Company. K. Nakagawa has received honoraria and C.H. Takimoto has received a commercial research grant from Eli Lilly and Company.

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