Pemetrexed Safety and Pharmacokinetics in Patients with Third-Space Fluid

Nicolas J. Dickgreber, Jens Benn Sorensen, Luis G. Paz-Ares, Tine Kjestrup Schytte, Jane E. Latz, Karen B. Schneck, Zheng Yuan, and José Miguel Sanchez-Torres

Abstract

Purpose: Pemetrexed is established as first-line treatment with cisplatin for malignant pleural mesothelioma and advanced nonsquamous non–small-cell lung cancer (NSCLC) and as single-agent second-line treatment for nonsquamous NSCLC. Because the structure and pharmacokinetics of pemetrexed are similar to those of methotrexate, and methotrexate is associated with severe toxicity in patients with third-space fluid (TSF), the safety of pemetrexed in patients with TSF was evaluated.

Experimental Design: Patients with TSF (pleural effusions, ascites) and relapsed, stage III/IV NSCLC or malignant pleural/peritoneal mesothelioma were treated with pemetrexed (500 mg/m²) on day 1 of each 21-day cycle. TSF was drained at any time only if clinically indicated. Plasma samples were collected during cycles 1 and 2 to compare pemetrexed concentrations with reference data from patients without TSF.

Results: Thirty-one patients with TSF received 123 pemetrexed doses (median, 4 cycles per patient; range, 1–11; mean dose intensity, 97.5%). Seven grade 3/4 drug-related toxicities, including four hematologic, were reported; there were no treatment-related deaths. There was no correlation between TSF amount and type, number, and sequelae of toxicities. Pemetrexed plasma concentrations were within the range of those in patients without TSF. Pemetrexed clearance and central volume of distribution were not statistically different between patients with and without TSF.

Conclusions: No clinically relevant alterations of pemetrexed pharmacokinetics occurred in patients with TSF. Pemetrexed was well tolerated; toxicities were expected and manageable. The standard pemetrexed dose recommendations were adequate for patients with TSF in this study. These data suggest that draining TSF before administering pemetrexed is unnecessary.

Corresponding Author: Nicolas J. Dickgreber, Hannover Medical School, Carl-Neuberg-Strasse 1, Hannover D-30625, Germany. Phone: 49-511-532-3692; Fax: 49-511-532-6575; E-mail: nicolas.dickgreber@gmx.de.

doi: 10.1158/1078-0432.CCR-09-3324

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Translational Relevance

This study examined the pharmacokinetics and safety of pemetrexed in patients with third-space fluid (TSF). The practice of draining TSF before pemetrexed administration was enacted based on structural and pharmacokinetic similarities between pemetrexed and methotrexate, which requires draining TSF, and without actual evidence of safety issues associated with administering pemetrexed to patients with TSF. Standard pemetrexed dose recommendations (starting dose and dose reductions) were adequate for patients with TSF treated in this study, suggesting that these patients can be treated with pemetrexed and obtain benefit, and that draining TSF before administering pemetrexed may not be necessary. Determining the necessity of draining TSF is important because the procedure is inconvenient, often painful, and introduces clinical risk due to potential procedural complications (e.g., pneumothorax, infection). These findings raise a broader question to consider in drug development: when and whether to draw analogies from prior observations versus limited information.

The differences in the pharmacokinetic/pharmacodynamic relationships for methotrexate and pemetrexed, coupled with information on pemetrexed MTD, suggest that draining TSF before pemetrexed administration may not be needed. Because draining TSF is inconvenient, often painful, and introduces clinical risk due to potential complications of the procedure (e.g., pneumothorax, infection), determining the necessity of drainage is clinically important.

To define the dosing and/or clinical practices required for patients with significant TSF (pleural effusions or ascites), a single-arm, open-label, phase II trial of single-agent pemetrexed in patients with TSF (pleural effusions or ascites) was conducted. Specifically, the safety and pharmacokinetics of pemetrexed were evaluated to determine (a) whether existing pemetrexed dosing recommendations (starting dose and dose reductions) were suitable for patients with TSF, and (b) whether draining TSF is necessary for patients before pemetrexed administration. A formal evaluation of efficacy was not an objective for this study.

Materials and Methods

Patient selection. Patients ≥18 years old with clinically detectable and stable-appearing TSF accumulations and either locally advanced or metastatic (stage III or IV) NSCLC or malignant pleural or peritoneal mesothelioma were eligible. In addition, patients must have had an Eastern Cooperative Oncology Group (24) performance status of 0 or 1, adequate bone marrow reserve and organ function, including calculated creatinine clearance >45 mL/min, and life expectancy ≥8 weeks. Previous treatment with one platinum-containing chemotherapy regimen in the locally advanced or metastatic setting was required for patients with NSCLC. Patients with mesothelioma could have received one previous chemotherapy regimen and could be enrolled if they were clinical candidates for treatment with single-agent pemetrexed in the investigator's opinion. Among reasons for exclusion were brain metastases, a concomitant serious systemic disorder, and inability or unwillingness to interrupt use of aspirin and other nonsteroidal anti-inflammatory drugs or to take folic acid, vitamin B12, or corticosteroids.

Institutional ethics review boards approved the protocol, and the trial was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent before treatment.

Treatment plan. This was a multicenter, open-label phase II study of single-agent pemetrexed with a target enrollment of 30 patients. Pemetrexed (500 mg/m²) was administered i.v. over 10 minutes on day 1 of each 21-day cycle. Chemotherapy was continued for a total of six cycles unless the investigator or patient opted to discontinue treatment. Patients could receive more than six cycles at the discretion of the treating physician and study sponsor. Patients received 4 mg of prophylactic dexamethasone unchanged drug in the urine (13, 14). Like methotrexate, the clearance of pemetrexed is decreased in patients with renal insufficiency (15, 16). For both drugs, decreased clearance results in greater systemic exposure, which may be associated with increased toxicity.

Although there are similarities between pemetrexed and methotrexate, there are sufficient differences in the pharmacokinetics and safety profiles of the two drugs to raise the question whether draining TSF before pemetrexed administration is necessary. Whereas methotrexate toxicity correlates with time above a concentration threshold (7), pemetrexed toxicity seems to correlate with total systemic exposure (AUC; refs. 14, 17–20). In addition, the terminal elimination half-life (t1/2) of methotrexate has been correlated with higher toxicity (7), whereas a similar correlation with pemetrexed has not been shown.

The maximum tolerated dose (MTD) for pemetrexed administered in combination with standard folic acid and vitamin B12 supplementation is a further indication that it may not be necessary to drain TSF before pemetrexed administration. The MTD for pemetrexed administered in combination with standard supplementation is 925 mg/m² or higher, depending on patient pretreatment status (lightly or heavily pretreated; ref. 21). This MTD corresponds to an 85% increase in drug exposure relative to the currently approved 500 mg/m² dose; thus, patients treated at 500 mg/m² could potentially tolerate an 85% increase in AUC without difficulty. This conclusion is supported by other studies which have shown that patients experience minimal additional toxicity with higher (900 and 1,000 mg/m²) pemetrexed doses (22, 23).
orally twice per day on the day before, the day of, and the
day after the first day of each cycle. Patients also received
oral folic acid (350-1,000 μg) daily and a vitamin B₁₂ injec-
tion (1,000 μg) every 9 weeks, beginning 1 to 2 weeks
before the first dose and continuing until 3 weeks after the
last dose of study treatment.

Dose adjustments at the start of a subsequent cycle of
study treatment were based on platelet and neutrophil na-
dir counts from the preceding cycle and on grade 3/4 non-
 hematologic toxicities from the preceding cycle. Patients
requiring a dose reduction received the reduced dose for
the remainder of the study. Patients who had two dose re-
ductions and who experienced toxicity requiring a third
dose reduction were discontinued from study therapy.
Cycles were delayed for up to 42 days to allow neutrophil
levels to return to ≥1.5 × 10⁹/L and platelet levels to return
to ≥100 × 10⁹/L. For grade 3/4 nonhematologic toxicities
(except for grade 3 transaminase elevation, nausea, and
vomiting), treatment was delayed until resolution to at
least the patient’s baseline. Patients received full suppor-
tive care therapies concomitantly during the study. Colony-
stimulating factors were administered according to the
American Society of Clinical Oncology guidelines (25). A
safety evaluation was done after 10 patients were enrolled
and treated with at least two cycles of pemetrexed.

Baseline and treatment assessments. Before entering the
study, patients underwent a medical history and physical
examination, and baseline tumor measurements were tak-
en for patients with measurable lesions. Measurable le-
sions were not required for study participation because
efficacy was not a primary or secondary end point. During
the study, lesion measurements were done at the discre-
tion of the investigator for patients showing evidence of
a response. Tumor response was assessed using the
Response Evaluation Criteria in Solid Tumors (26) and
summarized for all patients with available data.

All patients who received at least one dose of peme-
trexed were considered evaluable for safety. Toxicity was
assessed before each cycle according to the Common
Terminology Criteria for Adverse Events, version 3.0 (27).

Plasma samples for pemetrexed pharmacokinetic deter-
minations were collected from all patients during cycles
1 and 2 immediately before the end of infusion (9.5 minutes),
2 hours postinfusion, 9 to 10 hours postinfusion, 24 to
48 hours postinfusion, and 20 to 22 days postinfusion.
The extent of TSF was estimated immediately before
each cycle. Mild TSF was defined as a small amount of
fluid, less than moderate, and only detectable by radiolog-
ing imaging. Moderate TSF was defined as a medium
amount of fluid, with pleural effusions less than one third
of the way up the thorax on one side by imaging, and
with ascites detectable by physical exam. Severe TSF was
defined as a large amount of fluid, with pleural effusion
more than one third of the way up the thorax on imaging,
and with ascites detectable by visual appearance of the
abdomen. TSF was drained at any time during the study
if clinically indicated. If drainage was done, it was accom-
plished as completely as possible, the volume measured,
and a sample of the fluid collected to determine the peme-
trxed concentration. Additionally, a single plasma sample
was obtained at the time of drainage to determine the
corresponding plasma pemetrexed concentration.

Pharmacokinetic evaluations. Plasma and TSF sam-
ple were analyzed for pemetrexed concentrations
(Taylor Technology, Inc.) using a validated liquid
chromatography/electrospray ionization-tandem mass
spectrometry method to generate a linear response over
the concentration ranges of 10 to 2,000 ng/mL and 1,000

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**Fig. 1.** CONSORT flow diagram of patient disposition.
to 200,000 ng/mL (28). Pharmacokinetic analyses were done on a pooled data set containing pemetrexed concentration-time results from the current study combined with a reference data set (21) containing concentration-time results from patients without TSF. The data were analyzed by a population pharmacokinetics approach in the nonlinear mixed-effects modeling program NONMEM version VI with PREDPP (version V), using the first-order conditional estimation method with interaction (29–31). The pharmacokinetics of pemetrexed were described by a three-compartment model parameterized in terms of clearance (CL), central volume of distribution (V1), peripheral volume of distribution (V2 and V3), and intercompartmental clearances (Q1 and Q2), incorporating between-patient variability with respect to CL, V1, and V2, and a combined additive and proportional residual error term. The model included previously established covariates—Cockcroft-Gault creatinine clearance (32) with respect to CL, body surface area with respect to V1 and V2, and the model included previously established covariates—

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>Median (range) 63 (36-78)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>Median (range) 1.8 (1.4-2.3)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 27 (87) Female 4 (13)</td>
</tr>
<tr>
<td>Origin</td>
<td>Caucasian 30 (97) Hispanic 1 (3)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>NSCLC 23 (74) Mesothelioma 8 (26)</td>
</tr>
<tr>
<td>Primary basis for diagnosis</td>
<td>Cytologic 6 (19) Histopathologic 25 (81)</td>
</tr>
<tr>
<td>Disease stage</td>
<td>Stage III 12 (39) Stage IV 18 (58) Unknown 1 (3)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>0 14 (45) 1 17 (55)</td>
</tr>
<tr>
<td>Type of TSF</td>
<td>Pleural effusion 30 (97) Ascites 1 (3)</td>
</tr>
<tr>
<td>Baseline TSF severity*</td>
<td>Mild 15 (48) Moderate 14 (45) Severe 2 (6)</td>
</tr>
</tbody>
</table>

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

*Protocol definitions for qualitative estimate of TSF severity:
Mild—small amount of fluid; pleural effusion: detectable fluid on radiological imaging but less than moderate; ascites: can only be ascertained by radiological imaging (not detectable on physical exam). Moderate—medium amount of fluid; pleural effusion: less than one third of the way up the thorax on one side on imaging and obscuring the entire hemidiaphragm on that side; ascites: can be ascertained on physical examination (i.e., able to palpate a fluid wave). Severe—large amount of fluid; pleural effusion: more than one third of the way up the thorax on imaging; ascites: can be ascertained based on the visual appearance of the abdomen.
pharmacokinetic data are compared had a median age approximately 5 years younger, but with a similar age range. The reference population also had a similar PS 0/1 ratio, with most patients reporting prior chemotherapy and metastatic disease.

**Treatment**

The 31 patients received a median of four cycles (range, 1-11; 123 total cycles) of pemetrexed treatment. Among the 10 patients (32.3%) completing at least six cycles, 2 patients completed seven cycles and 1 patient completed 11 cycles; 15 patients (48.4%) discontinued the study before completing six cycles due to progressive disease (Fig. 1). The delivered dose intensity for pemetrexed was 97.5% (162.5 mg/m² per patient per week), with no dose omissions; however, one patient required a dose reduction due to asthenia not related to study drug, and there were four cycle delays due to adverse events (one each of asthenia, pain, pyrexia, and post-thoracentesis pneumothorax).

**Safety**

Seven grade 3 and 4 drug-related toxicities were reported; these included four hematologic toxicities, including one incident each of leukopenia, thrombocytopenia, neutropenia, and febrile neutropenia, and three nonhematologic toxicities, including one incident each of pulmonary pain, pleural effusion, and ascites. The patient who experienced grade 3/4 febrile neutropenia withdrew from the study due to this toxicity. The most frequently occurring grade 1/2 toxicities (>10% of patients) were nausea (9 patients, 29%), fatigue (7 patients, 22.6%), and anorexia (5 patients, 16.1%). There were no treatment-related deaths during the study or within 30 days of study discontinuation. Two patients died during the study from reasons judged by the investigators as non-treatment-related: respiratory failure following atrial fibrillation and dyspnea (day 22 of cycle 4 in a patient with NSCLC) and pneumonia (day 18 of cycle 1 in a patient with malignant pleural mesothelioma). One patient required a platelet transfusion during the study, and 5 (16%) patients required RBC transfusions due to grade 2 anemia, including 1 patient who had grade 2 anemia at baseline. Toxicities resulted in the hospitalization of 12 (39%) patients during the study and 2 (6%) patients within 30 days of study discontinuation. No correlation was observed between the volume of TSF (mild, moderate, severe) and the type, number, severity, or sequelae of toxicities (Table 2).

**Pharmacokinetic analyses**

**Observed pemetrexed plasma concentrations.** Figure 2 compares dose-normalized plasma pemetrexed concentration-versus-time data for patients with TSF treated in this study and a reference population consisting of patients without TSF (21). The concentration-versus-time data for the two studies were similar, indicating that pemetrexed pharmacokinetics were similar for the two groups of patients. All but one of the plasma samples scheduled to be collected during the 24- to 48-hour postinfusion interval were collected at approximately 24 hours; one sample collected at 48 hours was below the limit of detection. All 26 plasma samples collected at the end of cycle 1 and all but one of the 24 samples collected at the end of cycle 2 had pemetrexed concentrations below the quantification limit of <10 ng/mL. Likewise, in the reference study of patients without TSF, no patient had a quantifiable plasma concentration of pemetrexed at the end of a cycle. The single patient with TSF who had quantifiable pemetrexed concentrations at the end of cycle 2 did not have toxicities remarkably different from the other study participants.

**Evaluation of TSF status on pemetrexed pharmacokinetics.** Table 3 summarizes the evaluation of potential differences in pemetrexed pharmacokinetics based on TSF status. The three-compartment model did not support an interindividual variability term for V3, and thus a statistical comparison was not done and lack of a statistically significant difference was presumed. Pemetrexed CL and V2 were not significantly different between the two groups of patients.

<table>
<thead>
<tr>
<th>Table 2. Incidence of safety parameters by relative amount of TSF</th>
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<tbody>
<tr>
<td><strong>Total no. of pts with this safety measure</strong></td>
</tr>
<tr>
<td><strong>Patients with grade 3/4 hematologic toxicity</strong></td>
</tr>
<tr>
<td><strong>Patients with grade 3/4 nonhematologic toxicity</strong></td>
</tr>
<tr>
<td><strong>Patients who discontinued due to toxicity</strong></td>
</tr>
<tr>
<td><strong>Patients requiring transfusion</strong></td>
</tr>
<tr>
<td><strong>Patients hospitalized</strong></td>
</tr>
<tr>
<td><strong>Patient deaths</strong></td>
</tr>
</tbody>
</table>

Abbreviation: pts, patients.

*These toxicities were judged by the investigator as possibly related to study drug. Dose adjustments are not listed as a safety parameter because there were none judged as possibly related to study drug.
and without TSF, the 90% confidence intervals were within the predefined acceptance ranges of ±30%. A change in pemetrexed CL of 20% corresponds to an alteration in AUC of 25%. The C_{\text{max}} of patients in the two studies was similar due to the small difference (∼4%) in steady-state volume of distribution (V_{\text{ss}} = V_1 + V_2 + V_3), where the median (range) was 16.2 liters (10.3-25.7 liters) for patients in the reference study (21) and 16.8 liters (11.4-25.5 liters) for patients in this study.

There were no systematic changes in pemetrexed exposure as shown by model-predicted estimates of C_{\text{max}} (Fig. 3A) and AUC (Fig. 3B) over the course of two cycles, and no evident trend between pemetrexed exposure and the amount of TSF (mild to severe pleural effusions and moderate ascites). Only four patients had fluid drained before pemetrexed administration in cycle 2. These patients, all with adequate renal function, did not show a marked difference in pemetrexed pharmacokinetics in the presence or absence of TSF (Fig. 3). Pemetrexed concentrations in the four TSF samples were consistent with time-matched plasma samples, suggesting that pemetrexed does not accumulate in TSF relative to plasma.

**Efficacy**

Although efficacy was not an objective of this study and measurable disease was not required for study participation, baseline and postbaseline lesion measurements, if available, were reported by the investigator. Among the 22 patients with response data, there were no complete responses, 2 patients had a partial response, 8 patients had stable disease, and 12 patients had a best response of progressive disease. The other 9 patients had unknown response (including 1 patient with no baseline assessment, 7 patients with no postbaseline assessments, and 1 patient with unconfirmed stable disease).

**Discussion**

Because mesothelioma and advanced nonsquamous NSCLC often present with TSF accumulation, and its drainage introduces additional clinical risks, this single-arm, open-label, phase II trial of single-agent pemetrexed was undertaken to define the dosing and clinical practices required for patients with NSCLC or malignant pleural or peritoneal mesothelioma with TSF accumulation. A median of four cycles of the label-recommended dose of single-agent pemetrexed, 500 mg/m², administered as an i.v. infusion over 10 minutes on day 1 of each 21-day cycle,

**Table 3. Evaluation of potential differences in pemetrexed pharmacokinetics by presence of TSF**

<table>
<thead>
<tr>
<th>Parameter comparison*</th>
<th>ΔMOF †</th>
<th>Ratio (90% CI) ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL_{\text{TSF+}}/CL_{\text{TSF−}}</td>
<td>-0.019</td>
<td>1.01 (0.93-1.09)</td>
</tr>
<tr>
<td>V_{1\text{TSF+}}/V_{1\text{TSF−}}</td>
<td>-4.924</td>
<td>1.19 (1.04-1.36)</td>
</tr>
<tr>
<td>V_{2\text{TSF+}}/V_{2\text{TSF−}}</td>
<td>-1.699</td>
<td>1.10 (0.98-1.23)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CL, total systemic clearance; V1 and V2, central and peripheral pemetrexed volumes of distribution.

*Pharmacokinetic data from the current study of patients with TSF (TSF+) were compared with the reference study of patients without TSF (TSF−; ref. 21).

†The critical value of ΔMOF of −3.841 corresponds to P = 0.05.

‡The criteria for clinically relevant changes based on a log-normal distribution were ±20% (ratio of 0.8 to 1.25) for CL and ±30% (ratio of 0.7 to 1.43) for V1 and V2.
was safely given to patients with adequate renal clearance and standard vitamin supplementation without first draining the accumulated fluid. The toxicities that occurred were expected, manageable, and consistent with the known pemetrexed safety profile (33). This included four grade 3/4 hematologic toxicities and approximately 15–30% grade 1/2 fatigue, nausea, and anorexia. The dose delay and reduction recommendations provided in the pemetrexed label were adequate for patients with TSF who were treated in this study.

Plasma samples for measurement of pemetrexed concentrations were obtained after cycles 1 and 2, and pemetrexed concentration-versus-time results from this study were compared with those from a previously completed study in which single-agent pemetrexed was administered with vitamin supplementation to patients without TSF (21). The similar concentration-versus-time plots suggest that pemetrexed pharmacokinetics are comparable between patients with and without TSF. In addition, pemetrexed $C_{\text{max}}$ and AUC were consistent between cycles and were not affected by the draining of TSF. The relative amounts of TSF did not systematically correlate with any differences in pemetrexed pharmacokinetic parameters. Observations near the end of a cycle (19 days after pemetrexed dosing) were generally below the quantifiable limit, a finding that is consistent with the disposition of pemetrexed in patients without TSF. These results suggest that pemetrexed is not sequestered in third-space compartments and that the extent of exposure to pemetrexed is similar in patients with and without TSF.

The absence of overt differences in the safety profile or pharmacokinetics of pemetrexed administered to patients with TSF suggests that pemetrexed can be safely given to patients without draining the TSF. Furthermore, these
results indicated that the dosing guidelines previously established for patients without TSF are also applicable for patients with TSF. However, given that pemetrexed clearance is primarily through the kidneys, patients with marginal renal function might still require drainage. Indeed, a case report by Brandes and colleagues (34) found elevated levels of pemetrexed in plasma and ascites in a patient with renal failure following chemotherapy with cisplatin and pemetrexed. Although efficacy was not an objective of this study, lesion measurements were done at baseline, with subsequent measurements done at the investigator’s discretion. Among the 31 evaluable patients in this study, 2 patients showed a partial response and 8 patients, stable disease; 9 responses were unknown. Although the control of TSF by systemic chemotherapy has not been routinely described, chemotherapy is considered to potentially reduce TSF (and by extension, improve quality of life parameters associated with TSF accumulation; ref. 35).

Although this investigation examined pemetrexed administered as a single agent, it is coadministered with cisplatin for mesothelioma and advanced nonsquamous NSCLC (9, 12). Earlier work (33, 36, 37) examined possible pharmacokinetic interactions between pemetrexed and cisplatin and concluded that the two agents did not influence each other’s distribution or elimination. The pemetrexed pharmacokinetic results from this study were consistent with previous results for pemetrexed in combination with cisplatin, as well as those from single-agent pemetrexed studies (21, 28, 33, 36, 37). Thus, the results from the present study can likely be extended to patients receiving pemetrexed-cisplatin combination therapy (9, 12).

In addition to malignant pleural mesothelioma and NSCLC, pemetrexed has shown antitumor activity in a range of other solid malignancies including bladder, head and neck, breast, cervical, colorectal, pancreatic, and gastric cancers (38, 39). Some of these tumors may also present with TSF accumulations; for example, ascites is common in patients with gastrointestinal and gynecologic cancers, and pleural effusions may occur with breast cancer. Because the pharmacokinetics of pemetrexed have been characterized in patients with a variety of solid tumors and shown to be comparable across tumor types, the results from this study can likely be extended to patients with other tumors types and TSF accumulations.

Given the structural similarity of pemetrexed and methotrexate and the known alterations in pharmacokinetics and increased toxicity associated with methotrexate treatment of patients with TSF, this study examined pemetrexed treatment of patients with pleural effusions or ascites associated with NSCLC or mesothelioma. No clinically relevant differences in pemetrexed pharmacokinetics in patients with TSF were identified relative to a reference population of patients without TSF. The established dose of pemetrexed given with vitamin supplementation was well tolerated in patients with TSF, and the toxicities were consistent with the known pemetrexed safety profile. The standard dose recommendations (starting dose and dose reductions) for pemetrexed were adequate for patients with TSF who were treated in this study. Data from this study suggest that draining the TSF accumulations before pemetrexed treatment is not necessary. Further studies are warranted to confirm this finding.

**Disclosure of Potential Conflicts of Interest**

N.I. Dickgreber and J.B. Sorensen: commercial research support, honoraria from speakers bureau, and consultant/advisory board, Eli Lilly; L.G. Paz-Ares: consultant/advisory board, Eli Lilly. The other authors declare no conflicts.

**Acknowledgments**

We thank all the patients, investigators, and institutions involved in this study, and Mary Dungan Wood and Angela Lorio for writing and editorial assistance.

**Grant Support**

This study (H3E-MC-JMHX) was sponsored and funded by Eli Lilly and Company, Indianapolis, Indiana. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 12/18/2009; revised 03/19/2010; accepted 03/27/2010; published OnlineFirst 05/11/2010.

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Clinical Cancer Research

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Clin Cancer Res  Published OnlineFirst May 11, 2010.

Updated version  Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-09-3324

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