Pemetrexed Safety and Pharmacokinetics in Patients with Third-Space Fluid

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Abstract

\textbf{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.

\textbf{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/m\textsuperscript{2}) 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.

\textbf{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.

\textbf{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.

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Patients with thoracic tumors at diagnosis often present with imaging evidence of third-space fluid (TSF) such as malignant pleural effusions or ascites. TSF may alter the pharmacokinetics of methotrexate because it serves as an additional compartment into which the drug can be distributed and from which elimination can be delayed.

The pharmacokinetics of methotrexate are altered in patients with TSF. Methotrexate is significantly distributed into TSF and only slowly released, resulting in prolonged exposure of the terminal half-life of methotrexate in the plasma (3–5) and potentially increased toxicity (6). The toxicity of methotrexate for normal tissues is believed to depend on the duration of exposure to the drug above a threshold rather than on the peak level of drug achieved or overall exposure [i.e., area under the curve (AUC); refs. 7, 8]. The current clinical practice in patients with significant TSF accumulations is to drain the fluid before methotrexate treatment and to monitor plasma methotrexate levels.

Pemetrexed, a folate analogue metabolic inhibitor, has a chemical structure similar to methotrexate. It is indicated for locally advanced or metastatic nonsquamous non–small-cell lung cancer (NSCLC) as first-line therapy in combination with cisplatin (9), or as maintenance treatment for patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy (10), or after prior chemotherapy as a single agent (11). Additionally, pemetrexed in combination with cisplatin is indicated for treatment of mesothelioma (12).

Similar to methotrexate, the current practice in patients with TSF accumulations is to drain the fluid before pemetrexed administration. This practice is based on the structural and pharmacokinetic similarities between pemetrexed and methotrexate. The primary route of elimination for both pemetrexed and methotrexate is renal excretion of...
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 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.
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 injection (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 nadir counts from the preceding cycle and on grade 3/4 nonhematologic 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 reductions 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 supportive 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 taken for patients with measurable lesions. Measurable lesions 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 discretion 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 pemetrexed 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 determinations 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 radiologic 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 accomplished as completely as possible, the volume measured, and a sample of the fluid collected to determine the pemetrexed 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 samples 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 ng/mL to 250 μg/mL.

![Fig. 1. CONSORT flow diagram of patient disposition.](clincancerres.aacrjournals.org)
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 threecompartment 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, V1, and V2; and body surface area with respect to V1 and V2.

Potential differences in pemetrexed pharmacokinetics due to the presence of TSF were examined by adding this factor to the model as a covariate (dichotomous variable) with respect to CL, V1, and V2; nested models were compared based on the minimum objective function (MOF). Potentially significant alterations in pharmacokinetics were identified based on maximum likelihood criteria as those resulting in a decrease in the MOF of ≥3.841 points (P < 0.05 based on χ2 distribution with 1 degree of freedom) when added to the model. Parameter sensitivity analysis was used to define the 90% confidence interval for the ratio comparing pharmacokinetic parameters in patients with and without TSF. 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. Changes within these ranges result in pemetrexed exposures [AUC and maximum concentration (Cmax)] that remain lower than the exposures from the MTD (925 mg/m^2) established for pemetrexed with vitamin supplementation (21) and are shown to be tolerable (22, 23). The criteria for clinical relevance were based on AUC having been identified as the primary determinant of response in patients given pemetrexed (14, 17–20).

Results

Patients

The study was conducted at five study sites in Europe between December 26, 2006 and March 11, 2009. Thirty-one patients were enrolled in the study and received at least one dose of study drug (Fig. 1). Baseline and disease characteristics are summarized in Table 1. Twenty-seven men and four women were enrolled and treated in this study: 23 (74%) patients had a diagnosis of NSCLC and 8 (26%) had mesothelioma. Most patients (58%) had stage IV disease and mild (48%) or moderate (45%) amounts of TSF at baseline. For the majority of the patients (25 of the 31), the amount of TSF did not differ throughout the study, although 4 of the 25 had drainage done before a cycle. Three patients had a decrease in TSF while on study, and three additional patients had either an increase or both an increase and a decrease in TSF. The reference patient population (21) to which the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of patients (%)</th>
<th>N = 31</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>63 (36-78)</td>
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</tr>
<tr>
<td>Body surface area (m^2)</td>
<td>1.8 (1.4-2.3)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27 (87)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4 (13)</td>
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<tr>
<td>Origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>30 (97)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (3)</td>
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</tr>
<tr>
<td>Diagnosis</td>
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<td></td>
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<tr>
<td>NSCLC</td>
<td>23 (74)</td>
<td></td>
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<tr>
<td>Mesothelioma</td>
<td>8 (26)</td>
<td></td>
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<tr>
<td>Primary basis for diagnosis</td>
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<td></td>
</tr>
<tr>
<td>Cytologic</td>
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<td>Histopathologic</td>
<td>25 (81)</td>
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<td>Disease stage</td>
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<td>Stage IV</td>
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<td>14 (45)</td>
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<td>1</td>
<td>17 (55)</td>
<td></td>
</tr>
<tr>
<td>Type of TSF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>30 (97)</td>
<td></td>
</tr>
<tr>
<td>Ascites</td>
<td>1 (3)</td>
<td></td>
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<tr>
<td>Baseline TSF severity*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>15 (48)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>14 (45)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>2 (6)</td>
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</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 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 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).

Patients with grade 3/4 nonhematologic toxicity* 3 1 2 0
Patients with grade 3/4 hematologic toxicity* 4 3 0 1
Patients who discontinued due to toxicity 2 1 1 0
Patients requiring transfusion 5 4 0 1
Patients hospitalized 12 8 4 0
Patient deaths 2 2 0 0

<table>
<thead>
<tr>
<th>Table 2. Incidence of safety parameters by relative amount of TSF</th>
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<tr>
<td>Total no. of pts with this safety measure</td>
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<tr>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Patients with grade 3/4 hematologic toxicity*</td>
</tr>
<tr>
<td>Patients with grade 3/4 nonhematologic toxicity*</td>
</tr>
<tr>
<td>Patients who discontinued due to toxicity</td>
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<tr>
<td>Patients requiring transfusion</td>
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<tr>
<td>Patients hospitalized</td>
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<tr>
<td>Patient deaths</td>
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</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 (\sim 4%) in steady-state volume of distribution (V_{ss} = V1 + V2 + V3), 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,

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**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>
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<tr>
<td>CL_{TSF+}/CL_{TSF−}</td>
<td>−0.019</td>
<td>1.01 (0.93-1.09)</td>
</tr>
<tr>
<td>V1_{TSF+}/V1_{TSF−}</td>
<td>−4.924</td>
<td>1.19 (1.04-1.36)</td>
</tr>
<tr>
<td>V2_{TSF+}/V2_{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.

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