Phase I and Pharmacokinetic Study of Pemetrexed plus Cisplatin in Chemonaive Patients with Locally Advanced or Metastatic Malignant Pleural Mesothelioma or Non–Small Cell Lung Cancer

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Abstract

Purpose: Pemetrexed is approved as monotherapy and in combination with cisplatin. The established combination dose was identified before the addition of folic acid and vitamin B_{12} to the treatment regimen. We evaluated the toxicity and pharmacokinetics (PK) of higher pemetrexed doses with cisplatin and vitamin supplementation.

Experimental Design: Patients with malignant pleural mesothelioma or non–small cell lung cancer received pemetrexed doses from 500 to 900 mg/m^2 + 75 mg/m^2 cisplatin once every 21 days. Folic acid and vitamin B_{12} were administered per label recommendations.

Results: Twenty-one patients received a combined total of 84 cycles. The maximum tolerated dose was 900 mg/m^2 pemetrexed + 75 mg/m^2 cisplatin. Dose-limiting toxicities at this dose included grade 3 anemia, bronchopneumonia, and neutropenia, and 1 death from sepsis secondary to grade 4 febrile neutropenia, considered possibly related to study drugs. The recommended dose was 800 mg/m^2 pemetrexed + 75 mg/m^2 cisplatin. Pemetrexed PK were consistent across doses; pemetrexed did not seem to affect total or free platinum PK.

Conclusions: Pemetrexed with vitamin supplementation was safe and well tolerated at higher doses than the currently established 500 mg/m^2 + 75 mg/m^2 cisplatin. Based on this study, the recommended dose would be 800 mg/m^2 pemetrexed + 75 mg/m^2 cisplatin. However, recent studies showed a lack of improved efficacy for 900 or 1,000 mg/m^2 single-agent pemetrexed versus 500 mg/m^2 and a lack of PK/pharmacodynamic exposure-response relationship for the pemetrexed/cisplatin combination across pemetrexed exposures corresponding to this dose range. Based on currently available evidence, we recommend retaining the established dose.

Pemetrexed is an antifolate cytotoxic agent that has been approved in many countries in combination with cisplatin for first-line treatment of malignant pleural mesothelioma (MPM; ref. 1) and as single-agent therapy for second-line treatment of non–small cell lung cancer (NSCLC; ref. 2). Pemetrexed in combination with cisplatin has also been shown to be effective and well tolerated for first-line treatment of NSCLC (3) and was recently approved in Europe and the United States for that indication.

The currently established dose of 500 mg/m^2 pemetrexed in combination with 75 mg/m^2 cisplatin every 21 days was established based on a phase I study of pemetrexed in combination with cisplatin that was conducted without folic acid and vitamin B_{12} supplementation (4). During the pivotal phase III study, in which 500 mg/m^2 pemetrexed in combination with 75 mg/m^2 cisplatin was administered to patients with MPM (1), results from a multivariate regression analysis became available that indicated that an elevated baseline homocysteine level (consistent with subclinical folate deficiency) was highly correlated with more severe pemetrexed toxicities (5). To reduce the more severe drug-induced toxic effects, the protocol was amended to include supplementation of patients with folic acid and vitamin B_{12}. For all ongoing and subsequent studies of pemetrexed, supplementation was required. All patients enrolled in studies after December 1999 were instructed to take 350 to 600 μg folic acid or equivalent orally daily and received 1,000 μg vitamin B_{12} i.m. every 9 weeks, both beginning approximately 1 to 2 weeks before the first dose of pemetrexed and continuing until the patient completed pemetrexed therapy. Supplementation with folic acid and vitamin B_{12} is standard practice for treating patients with pemetrexed.

Supplementation improved the toxicity profile of pemetrexed (6–9) and led to the consideration that higher doses of pemetrexed might be safely administered. Subsequent phase I studies have shown that higher doses of single-agent pemetrexed are generally well tolerated when administered with vitamin supplementation (10, 11). The tolerability of higher doses of single-agent pemetrexed has also been confirmed in

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Translational Relevance

The study summarized below illustrates that, with folic acid and vitamin B_{12} supplementation, pemetrexed doses up to 800 mg/m^2 may be safely administered in combination with 75 mg/m^2 cisplatin. This dose represents a 50% increase from the established 500 mg/m^2 dose that was identified before the routine use of vitamin supplementation. This answers the tolerability question for higher pemetrexed doses combined with cisplatin when administered with vitamin supplementation and more fully defines the therapeutic window for the combination pemetrexed plus cisplatin regimen. These are important questions that remained unanswered at the time pemetrexed originally received regulatory approval. The well-established paradigm for cytotoxic chemotherapy is "more is better" up to the maximum tolerated dose. Currently available data suggest that "more is not necessarily better" for pemetrexed doses >500 mg/m^2. However, further investigation of whether specific patient subpopulations might benefit from higher doses of pemetrexed administered in combination with cisplatin may be warranted. Additionally, there may be individual patients for whom the treating physician perceives that a higher dose is warranted based on the patient's particular clinical circumstances. This study provides relevant and important information for physicians and investigators faced with these questions.

subsequent phase II and III clinical studies, although no additional efficacy benefit was shown (12, 13).

Pemetrexed is predominantly renally eliminated. Pharmacokinetic (PK) evaluations have shown that pemetrexed is ~80% protein bound, with rapid plasma distribution and elimination phases, and exhibits linear PK over a broad range of doses (0.2-1,400 mg/m^2). Pemetrexed is rapidly eliminated from the plasma by urinary excretion [half-life ($t_{1/2}$) = 3.5 hours], with about 70% to 90% of the administered dose recovered unchanged in the urine within 24 hours. The steady-state volume of distribution of pemetrexed is small (16 L), suggesting limited tissue distribution (10, 14, 15). Cisplatin is also renally eliminated and is highly protein bound (>90%). Most of the platinum derived from cisplatin is rapidly and irreversibly bound to plasma proteins. Whereas free platinum is rapidly eliminated from the plasma ($t_{1/2}$ = 0.5 hour), $t_{1/2}$ of total platinum is 5.4 days ± 1, reflecting the plasma protein binding (16).

The purpose of the current study was to determine if vitamin supplementation would enable pemetrexed to be given at doses higher than the currently approved 500 mg/m^2 in combination with a cisplatin dose of 75 mg/m^2. At the time the study was initiated, pemetrexed in combination with cisplatin had shown promising activity in chemonaive patients with advanced NSCLC and a phase III registration study was under way. Therefore, the results of the current study would be relevant to both MPM and NSCLC and the study was conducted in chemonaive patients with MPM or NSCLC. Additionally, by allowing enrollment of patients with either cancer type, patient availability was increased, thereby facilitating a more timely completion of the study than could have been accomplished had the patient population been limited to patients with MPM.

This study was conducted to establish the maximum tolerated dose (MTD) of pemetrexed plus cisplatin with vitamin supplementation. Secondary objectives included evaluating the safety profile of the combination of pemetrexed and cisplatin, identifying the recommended dose of pemetrexed with cisplatin for further study, and evaluating the PK of pemetrexed and total and free platinum in the presence of increasing doses of pemetrexed.

Materials and Methods

Eligibility criteria. Patients had either a histologic diagnosis of MPM or a histologic or cytologic diagnosis of stage IIIb or IV NSCLC. Measurable disease was required, and no prior systemic chemotherapy was allowed. Adequate organ function was required and defined as follows: bone marrow reserve—absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, hemoglobin ≥9 g/dL; hepatic function—bilirubin ≤1.5 times the upper limit of normal, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase ≤3.0 times normal, or an AST or ALT ≤5 times normal if due to malignant liver disease; and renal function—creatinine clearance ≥45 mL/min. Prior radiation was allowed to <25% of bone marrow, but patients who received prior whole-pelvis radiation and NSCLC patients who received prior radiotherapy for their current disease were not eligible.

The protocol was approved through institutional ethical review boards, and all patients provided written consent before receiving treatment. The study was conducted according to the most recent version of the Declaration of Helsinki or the applicable guidelines of good clinical practice, whichever provided the greater protection to the patient.

Study design. This open-label, phase I, dose-finding study of pemetrexed plus cisplatin was conducted in Germany at the Thoraxklinik-Heidelberg in Heidelberg, the Hannover Medical School in Hannover, and the Klinikum Nuernberg Nord in Nuremberg. The cisplatin dose was 75 mg/m^2 for all cohorts and the pemetrexed dose was increased in increments of 100 mg/m^2 for subsequent cohorts.

Treatment and dose escalation scheme. Pemetrexed and cisplatin were administered on day 1 of a 21-d cycle as i.v. infusions of 10 and 60 min, respectively. The decision to proceed to subsequent pemetrexed dose levels was based on dose-limiting toxicities (DLT) observed during cycle 1. Intrapatient dose escalation was not permitted. At least 1 patient with MPM was enrolled in each dose level to ensure adequate representation of MPM. The starting dose level was 500 mg/m^2 pemetrexed and 75 mg/m^2 cisplatin.

Table 1. Summary of patient demographics and characteristics

Characteristic	Patients (*n* = 21)
Median age, y (range)	65.6 (37.5-74.4)
Mean body weight, kg (range)	75.5 (46.4-108.0)
Gender, *n* (%)	
Male	15 (71.4)
Female	6 (28.6)
ECOG PS, *n* (%)	
0	10 (47.6)
1	11 (52.4)
Diagnosis, *n* (%)	
NSCLC	12 (57.1)
MPM	9 (42.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Table 2. Cycles administered by drug and dose level

DL	*n*	Pemetrexed/ cisplatin dose (mg/m^2)	Cycles administered, median (range)	Pemetrexed			Cisplatin		
				Planned dose, mean ($mg/m^2/wk$)*	Delivered dose, mean ($mg/m^2/wk$) †	Percentage of planned dose (delivered/ planned)	Planned dose, mean ($mg/m^2/wk$)*	Delivered dose, mean ($mg/m^2/wk$) †	Percentage of planned dose (delivered/ planned)
1	3	500/75	3.0 (2-6)	166.7	156.7	94.0	25.0	23.3	93.3
2	3	600/75	5.0 (1-6)	200.0	200.1	100.1	25.0	25.2	100.7
3	3	700/75	4.0 (4-4)	233.3	231.1	99.1	25.0	24.9	99.5
4 ‡	6	800/75	5.5 (2-6)	266.7	238.2	89.3	25.0	23.0	91.8
5 ‡	6	900/75	3.0 (1-6)	300.0	272.6	90.9	25.0	22.8	91.0

Abbreviation: DL, dose level.
*Planned mean dose = dose divided by 3 wk.
†Delivered mean dose = total dose divided by weeks on study.
‡Of the 14 cycle delays in this study, 12 occurred in dose levels 4 and 5, including 7 delays due to scheduling conflict and 1 delay due to inadequate folic acid compliance. The cycle delays contributed to the lower dose intensity seen in these two dose levels.

If three patients were enrolled at a given dose level without occurrence of a DLT during cycle 1, the next dose level was opened for accrual. If one patient experienced a DLT in cycle 1, three additional patients would be enrolled at that same dose level. If no further DLTs occurred in cycle 1, enrollment would proceed to the next dose level. If at least two patients experienced a DLT in cycle 1 at a given dose level, that dose level would become the MTD and patient enrollment did not proceed to higher dose levels. The recommended dose for further study would be one dose level below the MTD; however, drug-related adverse events occurring beyond cycle 1 were also considered when the recommended dose was determined.

DLTs were defined as grade 4 neutropenia lasting at least 7 d, febrile neutropenia (defined as grade 3 neutropenia and fever $\geq$38.5°C), grade 4 thrombocytopenia, grade 3 or 4 thrombocytopenia with grade 3 or 4 bleeding, any grade 3 or 4 nonhematologic drug-related toxicity (excluding nausea, vomiting, and transient grade 3 or 4 elevations in ALT or AST), or a cycle delay of >2 wk for grade 3 or 4 toxicity. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.[5]

Patients were required to take folic acid and vitamin B_{12} according to dosing instructions in the pemetrexed product labeling.[6,7] To reduce the incidence and severity of skin reactions, all patients began treatment with oral dexamethasone (4 mg twice daily) the day before pemetrexed cycles began and continued through the day after the 21-d cycle ended. In the absence of progressive disease or unacceptable toxicity, treatment was allowed up to six cycles. The routine use of granulocyte colony-stimulating factors was not allowed; however, granulocyte colony-stimulating factors could be administered after cycle 1 according to American Society of Clinical Oncology guidelines (17). Leucovorin was allowed for patients with grade 4 leukopenia or neutropenia lasting longer than 3 d, grade 4 thrombocytopenia, grade 3 thrombocytopenia with bleeding, or grade 3 or 4 mucositis.

Any patient experiencing a DLT in cycle 1 was to be discontinued from the study. Otherwise, dose delays of up to 21 d were permitted (i.e., up to 42 d between doses was allowed). ANC was required to be $\geq 1.5 \times 10^9$/L, platelets were required to be $\geq 100 \times 10^9$/L, creatinine clearance was required to be $\geq$45 mL/min, and other nonhematologic toxicities were required to resolve to less than or equal to the patient's baseline level before the next dose was administered. Up to two dose reductions were allowed; an adverse event requiring a third dose reduction required discontinuation from the study. Dose reductions were based on the worst grade of toxicity experienced during the cycle (including ANC and platelet nadirs). Both drugs were given at 75% of the previous dose for the following toxicities: grade 4 neutropenia plus grade $\leq$2 thrombocytopenia, grade 3 or 4 thrombocytopenia without bleeding (regardless of ANC), febrile neutropenia (regardless of platelets), grade $\geq$3 transaminase elevations, and grade $\geq$3 nonhematologic toxicities (except diarrhea and mucositis). Pemetrexed was given at 75% of the previous dose for grade $\geq$3 diarrhea and 50% of the previous dose for grade $\geq$3 mucositis with no change in the cisplatin dose. Both drugs were given at 50% of the previous dose for grade 3 or 4 thrombocytopenia with bleeding. Cisplatin was given at 50% of the previous dose for grade 2 neurosensory toxicities with no change in the pemetrexed dose; patients who experienced grade >2 neurosensory toxicities were to be discontinued from the study.

Baseline and treatment assessments. Before treatment and before each cycle, the following assessments were done: medical history (including documentation of concomitant medications), physical examination, performance status, toxicity grading, blood chemistries (including bilirubin, ALT, AST, alkaline phosphatase, serum creatinine, and magnesium), and calculation of creatinine clearance using the standard weight-based formula (18). Hematologic assessments were done weekly and included measurement of hemoglobin, leukocytes, platelets, and neutrophils (sum of segmented and bands). Tumor assessments were conducted before treatment and at every other cycle. Measurement of tumor lesions, timing of tumor assessments, and assessment of response were based on Response Evaluation Criteria in Solid Tumors for NSCLC (19) and modified Response Evaluation Criteria in Solid Tumors for MPM (20). Per the protocol, the collection of efficacy data was limited to the assessment of best overall response. After completion of study drug treatment, patients were not followed to assess time to disease progression or survival time.

PK methods. PK sampling was done on all enrolled patients. Samples were drawn from the arm contralateral to the infusion line. Heparinized blood samples were collected during cycle 1 for the measurement of concentrations of pemetrexed, free platinum, and total platinum after the start of the pemetrexed dose administration. Plasma samples for pemetrexed and platinum (total and free platinum) measurement were collected at 9 min (1 min before the end of the pemetrexed infusion), 40 min (immediately before the cisplatin infusion), 70 min (halfway through the cisplatin infusion), 100 min (just before the end of the cisplatin infusion), and at 3, 4, 6, 8, 12, 24, and 48 h after the start of the

[5] http://ctep.cancer.gov
[6] http://pi.lilly.com/us/alimta-pi.pdf
[7] http://www.emea.europa.eu/humandocs/Humans/EPAR/alimta/alimta.htm

Table 3. DLTs and other grade 3/4 drug-related Common Terminology Criteria for Adverse Events

Dose level	Pemetrexed/ cisplatin dose (mg/m^2)	DLTs	Other grade 3*	Other grade 4*
1 (n = 3)	500/75	None	Leukopenia Thrombocytopenia	None
2 (n = 3)	600/75	None	Decreased creatinine clearance	None
3 (n = 3)	700/75	Grade 4 thrombocytopenia (cycle 3)	Hypocalcemia Leukopenia Neutropenia Hearing loss	Lymphopenia
4 (n = 6)	800/75	None	None	None
5 (n = 6)	900/75	Grade 4 febrile neutropenia † (cycle 2) and grade 5 sepsis † (cycle 2) Grade 3 anemia ‡ (cycle 1) and grade 3 bronchopneumonia ‡ (cycle 1) Grade 3 anemia ‡ (cycle 2), grade 3 bronchopneumonia ‡ (cycle 2), and grade 3 neutropenia ‡ (cycle 2)	Neutropenia (2 incidences) Vomiting	None

*National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Number of incidences = 1 unless otherwise indicated.
†Although the protocol-defined determination of MTD was based on cycle 1 DLTs, the severity of these cycle 2 DLTs prompted the investigators to declare dose level 5 the MTD. This patient was hospitalized for the DLT of grade 4 febrile neutropenia and ultimately died due to grade 5 sepsis.
‡These five events occurred in the same patient. According to the protocol, the patient should have been discontinued from therapy after the DLTs in cycle 1; therefore, the DLTs experienced by the patient in cycle 2 are also reported.

pemetrexed infusion. Additional samples for platinum were collected at 72, 192, 360, and 504 h after the start of pemetrexed infusion. After initial analyses showed that free platinum concentrations decreased to undetectable levels after ~12 h, the collection of samples for free platinum beyond 24 h after the pemetrexed infusion was eliminated. Heparinized human plasma samples were analyzed for pemetrexed using validated liquid chromatography electrospray ionization with tandem mass spectrometric detection methods over the concentration ranges of 10 to 2,000 ng/mL and 1,000 to 200,000 ng/mL (Taylor Technology, Inc.). Heparinized plasma samples were analyzed for total platinum and free platinum derived from cisplatin using a validated inductively coupled plasma mass spectrometry method over the concentration range of 50 to 2,000 ng/mL (Cantest Ltd.).

PK evaluation of pemetrexed and total platinum concentration-time data was done using noncompartmental methods with WinNonlin Enterprise, version 5.0.1 (Pharsight). PK parameters determined were maximum plasma concentration (C_{max}), elimination $t_{1/2}$, area under the plasma concentration versus time curve from time 0 to infinity ($AUC_{0-\infty}$), volume of distribution at steady state (V_{ss}), and total systemic clearance (CL). Pemetrexed PK in the current study were compared with single-agent pemetrexed PK (10).

Total platinum concentrations from the current study were compared with reference data from the previous phase III study that evaluated the pemetrexed/cisplatin combination (1). Because free platinum concentrations were not measured in that study, an established population PK model for free platinum (21) was used to simulate the expected unbound platinum concentration-time profiles for 500 patients given a 1-h infusion of 75 mg/m^2 cisplatin using NONMEM, version 5 (22). The free platinum concentrations from this study were then compared by overlay plot with these simulated free platinum concentrations.

Statistical methods. Efficacy was not a primary end point of this phase I study, and the sample size was limited in each of the dose levels (three to six patients per cohort); therefore, no formal statistical analyses of efficacy were done. Investigator-assessed tumor response was reported and summarized. There were no a priori controls for dose assignment to patients.

All patients treated with at least one dose of pemetrexed were included in the assessment of safety. All enrolled patients who had a histologic diagnosis of MPM or histologic or cytologic diagnosis of NSCLC, no concurrent systemic chemotherapy, and treatment with at least one dose of pemetrexed were evaluated for tumor response to document evidence of antitumor activity.

Results

Patient characteristics. Twenty-one patients (12 with NSCLC and 9 with MPM) were enrolled in this study between November 21, 2005, and April 16, 2007. They completed a combined total of 84 cycles of treatment (range, 1-6 cycles per patient). Patients were 71.4% male and 100% Caucasian; 57.1% had a diagnosis of NSCLC. Patient characteristics are

Table 4. Best overall response by dose and cancer type

Dose level	Pemetrexed/ cisplatin dose (mg/m^2)	Partial response		Stable disease		Progressive disease		Unknown	
		NSCLC	MPM	NSCLC	MPM	NSCLC	MPM	NSCLC	MPM
1 (n = 3)	500/75	1	1	1					
2 (n = 3)	600/75		1	2					
3 (n = 3)	700/75			1		1			1
4 (n = 6)	800/75	1	1	2	1		1		
5 (n = 6)	900/75			2	2		1	1	

summarized in Table 1. Reasons for discontinuation from the study included protocol completion (i.e., the patient received six cycles of study drug; $n = 6$), adverse event ($n = 6$), progressive disease ($n = 5$), patient decision ($n = 3$), and death ($n = 1$).

Dose administration. Patients were enrolled in five dose levels, with the pemetrexed dose ranging from 500 to 900 mg/m^2 (Table 2). Three patients had dose reductions during the study. Two patients had reductions of both pemetrexed and cisplatin for anemia (one patient at 900 mg/m^2 + 75 mg/m^2) and thrombocytopenia (one patient at 700 mg/m^2 + 75 mg/m^2), and a third patient had two pemetrexed reductions from 800 mg/m^2 for gastric ulcer. Drug-related events caused seven cycle delays; reasons included neutropenia, anemia, increased ALT, bronchopneumonia, and gastric ulcer. Three delays occurred in the 500 mg/m^2 + 75 mg/m^2 group, two delays in the 800 mg/m^2 + 75 mg/m^2 group, and two delays in the 900 mg/m^2 + 75 mg/m^2 group. One cycle was delayed because the patient failed to take the minimum required amount of folic acid between cycles (800 mg/m^2 + 75 mg/m^2). Scheduling conflicts accounted for an additional seven cycle delays, all of which occurred in patients receiving 800 or 900 mg/m^2 of pemetrexed. Thus, the lower dose intensities in the 800 and 900 mg/m^2 dose groups (Table 2) reflect the higher incidence of dose reductions and cycle delays in those treatment groups.

Dose-limiting toxicities. DLTs are summarized in Table 3. Although the protocol defined the MTD as the dose level at which at least two patients experience DLTs in cycle 1, the DLTs of grade 4 febrile neutropenia and grade 5 sepsis (i.e., death due to sepsis) experienced by one patient in cycle 2 were considered of sufficient severity to warrant determination of 900 mg/m^2 pemetrexed plus 75 mg/m^2 cisplatin to be the MTD. The six patients treated with 800 mg/m^2 pemetrexed plus 75 mg/m^2 cisplatin experienced no DLTs. Therefore, based on these results, the recommended dose for further study was 800 mg/m^2 pemetrexed plus 75 mg/m^2 cisplatin.

Toxicity. Drug-related grade 3/4 toxicities other than DLTs are also included in Table 3. The most commonly occurring grade 3/4 toxicity was neutropenia, reported in five patients (23.8%), which occurred at dose levels 3 and 5 (700 and 900 mg/m^2 of pemetrexed, respectively). One patient had a grade 3 infection; one patient died of sepsis resulting from an infection. No other deaths occurred during the study or the 30-day follow-up period. Six patients (28.6%) discontinued the study because of adverse events: two from serious adverse events (anemia and abnormal hearing test results) and four from nonserious adverse events [decreased creatinine clearance (2 patients), tinnitus (1 patient), and leukopenia (1 patient)].

Tumor response. Best overall responses are presented in Table 4. Five of 21 patients [3 of 9 (33%) with MPM and 2 of 12 (17%) with NSCLC] had partial responses, and 11 [3 of 9 (33%) with MPM and 8 of 12 (67%) with NSCLC] had stable disease. Three patients (two with MPM and one with NSCLC) had progressive disease and two patients had an unknown best response. Partial responses occurred in dose levels 1, 2, and 4. There were no overt differences in efficacy across the dose groups.

Pharmacokinetics. Pemetrexed and platinum plasma concentration data were evaluated for all 21 patients enrolled in the study. For each of the analytes, C_{max} occurred at the end of the infusion as expected, and the multiexponential decay in the PK profiles from patients in the current study was similar to those seen previously (Fig. 1; refs. 10, 21).

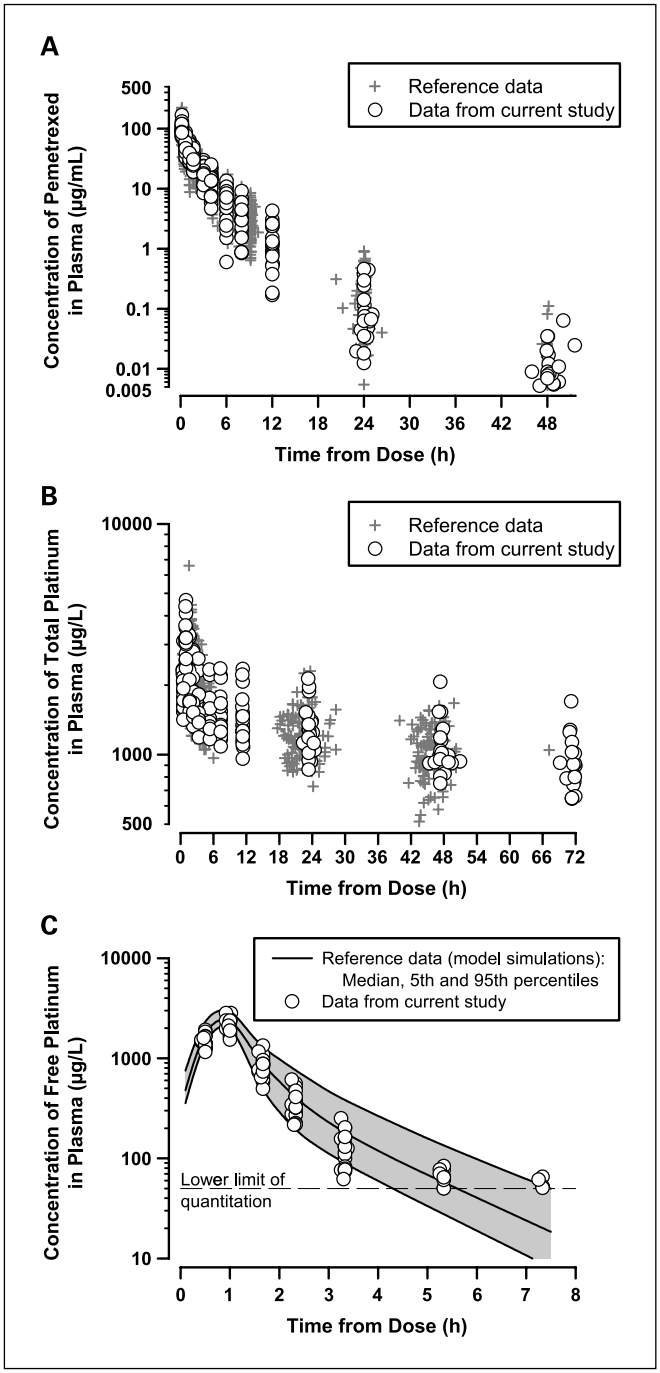

Fig. 1. Plasma concentration-time profile from the start of infusion for pemetrexed (*A*), total platinum (*B*), and free platinum (*C*).

Pemetrexed clearance did not show dose dependency (Table 5), indicating that pemetrexed PK were linear over this dose range. Pemetrexed exposure (AUC) increased in a dose proportional manner over the dose range of 500 to 900 mg/m^2 when administered in combination with 75 mg/m^2 cisplatin; dose-normalized pemetrexed concentrations were within the range of those seen in previous single-agent pemetrexed studies. The PK paremeters (Table 5) for pemetrexed are also consistent with those reported for single-agent pemetrexed administration (10), suggesting that cisplatin coadministration

did not alter pemetrexed PK across the range of doses administered in this study.

Total platinum PK were consistent across the dose groups (Table 5), indicating that increasing doses of pemetrexed did not alter the PK of total platinum derived from cisplatin. Although the mean exposure of free platinum seemed to decrease with increasing doses of pemetrexed, it is important to note that free platinum is renally eliminated and that the patients in dose levels 4 and 5 had higher creatinine clearance (i.e., better renal function) relative to those in the other cohorts. Further examination of the individual patient exposure data with the corresponding creatinine clearance values by regression analysis illustrated that exposure was lower for patients with higher creatinine clearance (figure not shown). Therefore, as would be expected for a renally eliminated drug, the lower platinum exposures in the higher dose levels reflect higher platinum clearance resulting from the increased renal function in these patients relative to those in the other cohorts. Thus, the decrease in free platinum C_{max} in the higher cohorts is not due to the higher doses of pemetrexed causing alteration in platinum PK but rather is a reflection of the coincidental enrollment of patients with better renal function in the higher dose cohorts.

Discussion

The currently established dose of 500 mg/m^2 pemetrexed in combination with 75 mg/m^2 cisplatin for the first-line treatment of MPM was initially identified in a phase I study without vitamin supplementation (4). After a programmatic decision was made to supplement all patients receiving pemetrexed with folic acid and vitamin B_{12}, and efficacy and safety were established for the 500 mg/m^2 dose with vitamin supplementation, phase I dose-escalation studies of single-agent pemetrexed with vitamin supplementation in patients with solid tumors (10, 11) showed that higher doses of pemetrexed could be administered without intolerable toxicities. Additional analyses of MPM and NSCLC studies of pemetrexed with folic acid and vitamin B_{12} supplementation have also shown a reduction in severe drug-related toxicities (6–9).

This is the first study to show that pemetrexed at doses higher than 500 mg/m^2 in combination with 75 mg/m^2 cisplatin every 21 days can be safely administered and is well tolerated when accompanied by vitamin supplementation. A total of 21 patients were enrolled in five dose levels, 500 to 900 mg/m^2 of pemetrexed in combination with 75 mg/m^2 cisplatin. The MTD was 900 mg/m^2 pemetrexed plus 75 mg/m^2 cisplatin with vitamin

Table 5. Summary of PK parameters for pemetrexed and platinum (total and free) derived from cisplatin

	Dose level 1	Dose level 2	Dose level 3	Dose level 4	Dose level 5	Overall
Pemetrexed dose (mg/m^2)	500	600	700	800	900	NA
n	3	3	3	6	6	21
BSA, m^2*	1.71	1.58	1.93	1.77	1.98	1.82
(range)	(1.43-1.91)	(1.46-1.82)	(1.51-2.19)	(1.54-1.96)	(1.88-2.08)	(1.43-2.19)
Baseline CrCL, mL/min*	69.9 †	72.6	78.1	99.0	102	89.7 ‡
(range)	(48.3-91.4)	(43.1-109)	(52.5-102)	(57.9-139)	(72.3-134)	(43.1-139)
Pemetrexed						
Total dose, mg*	870	970	1,420	1,430	1,820	NA
(range)	(734-979)	(894-1,120)	(1,280-1,530)	(1,200-1,580)	(1,730-1,890)	
C_{max}, μg/mL§ (CV%)	113 (20)	122 (9)	156 (9)	154 (16)	180 (18)	NA
$AUC_{0-\infty}$, μg·h/mL§ (CV%)	261 (5)	188 (41)	267 (37)	279 (14)	299 (24)	NA
CL, mL/min§ (CV%)	55.3 (13)	85.5 (43)	88.6 (29)	84.9 (14)	101 (25)	NA
V_{ss}, L§ (CV%)	13.1 (34)	12.8 (22)	16.4 (15)	13.2 (22)	16.9 (20)	NA
$t_{1/2}$, h§	3.39	2.91	3.29	2.76	3.25	NA
(range)	(2.74-3.78)	(2.62-3.36)	(2.82-4.28)	(2.59-2.92)	(2.63-5.20)	
Cisplatin total dose, mg* (range)	129 (110-140)	120 (110-140)	143 (112-160)	132 (110-148)	146 (140-153)	135 (110-160)
Total platinum						
C_{max}, μg/mL§ (CV%)*	3.48 (10)	3.18 (16)	3.26 (13)	2.93 (10)	3.21 (15)	3.17 (13)
$AUC_{0-\infty}$, μg·h/mL§ (CV%)*	310 (19)	334 (30)	238 (24)	287 (12)	247 (13)	277 (20)
CL, L/h/m^2§ (CV%)*	0.244 (17)	0.227 (31)	0.313 (26)	0.260 (14)	0.299 (13)	0.270 (20)
V_{ss}, L/m^2§ (CV%)*	43.6 (10)	44.1 (15)	48.4 (14)	47.4 (14)	51.4 (11)	47.6 (13)
$t_{1/2}$, h§	75.2	108	80.1	88.9	86.6	87.2
(range)	(72.3-78.1)	(73.6-159)	(71.8-87.3)	(60.1-110)	(69.8-111)	(60.1-159)
Free platinum						
C_{max}, μg/mL§ (CV%)*	2.24 (40)	2.35 (18)	2.25 (13)	1.97 (19)	1.88 (27)	2.07 (23)
$AUC_{0-\infty}$, μg·h/mL§ (CV%)*	3.45 (33)	3.23 (27)	3.27 (4)	2.77 (16)	2.61 (16)	2.94 (21)
CL, L/h/m^2§ (CV%)*	21.9 (30)	23.5 (27)	22.7 (4)	27.0 (18)	28.3 (17)	25.4 (21)
V_{ss}, L/m^2§ (CV%)*	28.0 (3)	21.5 (23)	28.1 (29)	23.4 (26)	25.9 (20)	25.1 (22)
$t_{1/2}$, h§	0.845	0.640	1.04	0.631	0.768	0.749
(range)	(0.643-0.970)	(0.514-0.951)	(0.970-1.11)	(0.476-1.00)	(0.590-1.13)	(0.476-1.13)

Abbreviations: NA, not applicable; BSA, body surface area; CrCL, creatinine clearance based on Cockcroft-Gault method; CV%, coefficient of variation as percentage.
*Arithmetic mean.
†n = 2.
‡n = 20.
§Geometric mean.

supplementation and the recommended dose, therefore, was 800 mg/m^2 pemetrexed plus 75 mg/m^2 cisplatin. Generally, the toxicities were mild and manageable, with only one DLT observed in the first four dose levels. The main toxicities were hematologic, with grade 3/4 neutropenia being most common, consistent with the rate in supplemented patients in the phase III study of the combination in MPM (1). Overall, the safety and efficacy results observed in this study were consistent with the known safety and efficacy profiles of this combination.

Pemetrexed PK in the current study were similar to those observed in several previous studies: an analysis of 10 phase II single-agent studies in which pemetrexed doses of 500 and 600 mg/m^2 were administered (15), a large phase I single-agent study in which pemetrexed doses of 600 to 1,400 mg/m^2 were administered (10), and the large phase III registration study in MPM that used doses of 500 mg/m^2 pemetrexed and 75 mg/m^2 cisplatin (1).

Total platinum PK in the current study were also comparable with those observed in both the single-agent cisplatin and combination pemetrexed and cisplatin groups in the large phase III registration study of pemetrexed and cisplatin in MPM.[6] Because the pharmacodynamic (PD) effects of cisplatin (efficacy and toxicity) are considered to be a result of the free platinum concentrations (23), free platinum was measured in this study to determine if there were any alterations in free platinum concentrations with increasing exposures of pemetrexed. The observed free platinum concentrations in the current study were consistent with those predicted based on an established population PK model (21), thereby suggesting that pemetrexed does not cause any changes in free platinum concentrations.

Although the recommended dose from this study (800 mg/m^2 pemetrexed plus 75 mg/m^2 cisplatin) was safely given to and well tolerated by patients, it is important to consider these results in the context of other recently published research. Results from two recently completed, randomized studies showed that neither 900 mg/m^2 (12) nor 1,000 mg/m^2 (13) single-agent pemetrexed with vitamin supplementation showed improved efficacy relative to the established 500 mg/m^2 dose. It is not known how these single-agent results relate to the efficacy of higher doses of pemetrexed in combination with cisplatin. PK/PD exposure-response analyses based on the pivotal phase III study of the pemetrexed and cisplatin combination for the treatment of MPM (1) similarly suggested a lack of increased efficacy with increasing pemetrexed exposure (24). Although the phase III MPM study used a single dose of pemetrexed (500 mg/m^2), because of individual variation in body surface area and renal function, a range of exposures was seen, including those expected for the 900 mg/m^2 dose. Multiple regression was not significant for an effect of AUC on time to progressive disease and overall survival (P values of 0.692 and 0.391, respectively), indicating a lack of an exposure-response relationship and suggesting a lack of increased efficacy with increased dose. Overall, these recently published results suggest that the recommended dose from this study may not provide an efficacy advantage over the established dose of 500 mg/m^2 pemetrexed and 75 mg/m^2 cisplatin.

In conclusion, the current study shows that, in chemonaive patients with locally advanced or metastatic MPM or NSCLC, pemetrexed in combination with 75 mg/m^2 cisplatin every 21 days with vitamin supplementation is safely administered and well tolerated at doses higher than 500 mg/m^2. The MTD was 900 mg/m^2 pemetrexed plus 75 mg/m^2 cisplatin. Given the efficacy results from other recent studies and recently reported PK/PD exposure-response analyses, however, we recommend retaining the currently established dose of 500 mg/m^2 pemetrexed and 75 mg/m^2 cisplatin administered every 21 days with vitamin supplementation.

Disclosure of Potential Conflicts of Interest

N.J. Dickgreber, T.H. Fink, and M. Thomas have received a commercial grant and honoraria from Eli Lilly and Company. J.E. Latz, A.M. Hossain, and L.C. Musib are employed by and have an ownership interest in Eli Lilly and Company.

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