Phase III Study of Pemetrexed in Combination With Cisplatin Versus Cisplatin Alone in Patients With Malignant Pleural Mesothelioma

By Nicholas J. Vogelzang, James J. Rusthoven, James Symanowski, Claude Denham, E. Kaukel, Pierre Ruffie, Ulrich Gatzemeier, Michael Boyer, Salih Emri, Christian Manegold, Clet Niyikiza, and Paolo Paoletti

Purpose: **Patients with malignant pleural mesothelioma, a rapidly progressing malignancy with a median survival time of 6 to 9 months, have previously responded poorly to chemotherapy. We conducted a phase III trial to determine whether treatment with pemetrexed and cisplatin results in survival time superior to that achieved with cisplatin alone.**

Patients and Methods: **Chemotherapy-naive patients who were not eligible for curative surgery were randomly assigned to receive pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 on day 1, or cisplatin 75 mg/m^2 on day 1. Both regimens were given intravenously every 21 days.**

Results: **A total of 456 patients were assigned: 226 received pemetrexed and cisplatin, 222 received cisplatin alone, and eight never received therapy. Median survival time in the pemetrexed/cisplatin arm was 12.1 months versus 9.3 months in the control arm ($P = .020$, two-sided log-rank test). The hazard ratio for death of patients in the pemetrexed/cisplatin arm versus those in the control arm was 0.77. Median time to progression was significantly longer in the pemetrexed/cisplatin arm: 5.7 months versus 3.9 months ($P = .001$). Response rates were 41.3% in the pemetrexed/cisplatin arm versus 16.7% in the control arm ($P < .0001$). After 117 patients had enrolled, folic acid and vitamin B_{12} were added to reduce toxicity, resulting in a significant reduction in toxicities in the pemetrexed/cisplatin arm.**

Conclusion: **Treatment with pemetrexed plus cisplatin and vitamin supplementation resulted in superior survival time, time to progression, and response rates compared with treatment with cisplatin alone in patients with malignant pleural mesothelioma. Addition of folic acid and vitamin B_{12} significantly reduced toxicity without adversely affecting survival time.**

J Clin Oncol 21:2636-2644.

MALIGNANT PLEURAL mesothelioma (MPM) is a locally invasive and rapidly fatal malignancy linked to asbestos exposure. Surgical resection is possible in a minority of patients, and fewer than 15% of these patients live beyond 5 years.[1-3] For those who are not treated with curative resection, the median survival duration when receiving supportive care alone has been reported as 6 months,[4,5] whereas the median survival time of 337 patients in 11 multicenter chemotherapy trials was 7 months.[6] Treatment with radiation therapy has been equally disappointing, in part because of difficulties in irradiating disease while avoiding toxicity to normal lung, cardiac, and spinal cord tissues.[7,8]

Numerous single agents, such as cisplatin, doxorubicin, and gemcitabine, and drug combinations, such as gemcitabine and cisplatin, have been studied in phase II trials.[9-14] However, the strength of this evidence has not supported the standard use of chemotherapy. The few published randomized trials in MPM have shown negative results, have often been underpowered, and have been associated with median survival times of only 6 to 8 months.[15-19]

Recently, pemetrexed, a novel multitargeted antifolate,[20] has shown modest activity as a single agent in a phase II trial of patients with MPM (response rate, 14.1%, or nine of 64 patients).[21] Pemetrexed inhibits dihydrofolate reductase, thymidylate synthase, and glycinamide ribonucleotide formyltransferase, enzymes involved in purine and pyrimidine synthesis.[22,23] Pemetrexed enters the cell primarily through the reduced folate carrier, and undergoes extensive intracellular polyglutamation by folylpoly-gamma-glutamate synthetase. The polyglutamated forms, retained for long periods within the cell,[24] have more than 100-fold greater affinity for thymidylate synthase and glycinamide ribonucleotide formyltransferase than the parent drug, pemetrexed monoglutamate.[25] In addition to single-agent activity, responses were seen in MPM patients in two phase I trials of pemetrexed combined with platinum analogs.[26,27] In the first study of 40 assessable patients, 11 patients were enrolled with a diagnosis of MPM and were given pemetrexed combined with cisplatin, at increasing doses of both drugs. Surprisingly, five (45%) of 11 patients had a partial response (PR). The maximum-tolerated dose over all cycles was established at pemetrexed 600 mg/m^2 and cisplatin 75 mg/m^2. At this dose, seven of 12 patients experience grade 3 or 4 neutropenia, whereas eight patients experienced grade 3 or 4 anemia. This was in contrast to only one of three patients with grade 3 neutropenia or grade 4 anemia treated at the recommended phase II dose of

From the University of Chicago Cancer Research Center, Chicago, IL; Eli Lilly and Company, Indianapolis, IN; US Oncology, Dallas, TX; Allgemeines Krankenhaus Harburg, Hamburg; Krankenhaus Großhansdorf, Großhansdorf; and Thoraxklinik-Rohrbach, Heidelberg, Germany; Institut Gustave Roussy, Villejuif, France; Royal Prince Alfred Hospital, Camperdown, Australia; and Hacettepe University Medical Faculty, Ankara, Turkey.

Submitted November 26, 2002; accepted February 21, 2003.

Supported by a grant from Eli Lilly and Company.

Address reprint requests to Nicholas J. Vogelzang, MD, University of Chicago, Cancer Research Center, 5841 South Maryland Ave, Chicago, IL 60637; email: nvogelza@medicine.bsd.uchicago.edu.

0732-183X/03/2114-2636/$20.00

DOI: 10.1200/JCO.2003.11.136

pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2. The second trial enrolled 25 chemotherapy-naive patients with MPM who received increasing doses of both pemetrexed and carboplatin; eight patients (32%) assessable for response experienced a PR.

Encouraged by these results and by early results of a phase II trial of pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 in patients with non–small-cell lung cancer showing that the combination at this dose was well tolerated,[28] we initiated a large, phase III clinical trial to determine whether pemetrexed/cisplatin therapy was associated with superior survival duration compared with cisplatin alone in the treatment of patients with MPM.

PATIENTS AND METHODS

Patients

Patients with histologically proven pleural mesothelioma who were not candidates for curative surgery were assessed for eligibility. Eligibility requirements included uni- or bidimensionally measurable disease, age ≥18 years with life expectancy ≥12 weeks, and a Karnofsky performance status of ≥ 70. Patients were excluded if they had prior chemotherapy, a second primary malignancy, or brain metastases, or if they were unable to interrupt nonsteroidal anti-inflammatory drugs.

Study Design

This study was a multicenter, randomized, single-blind study comparing treatment with pemetrexed and cisplatin versus cisplatin alone in MPM patients. The primary outcome was survival. Secondary outcomes reported here include time to progressive disease, time to treatment failure, tumor response rate, and duration of response. Pulmonary function testing, lung density analysis, and quality-of-life outcomes will be reported in separate publications. After informed consent was obtained, eligible patients were randomly assigned to arms of pemetrexed and cisplatin or cisplatin alone. Patient randomization was balanced for the following baseline factors: treatment center, country, pain level at entry, analgesic consumption at entry, dyspnea at entry, performance status, degree of measurability of disease, histologic subtype, sex, baseline WBC count, and baseline serum homocysteine levels.

Three treatment-related deaths (7%) were reported among the first 43 patients randomly assigned to the experimental arm. Severe toxicities (eg, grade 4 neutropenia and diarrhea) in other pemetrexed studies were linked to high blood levels of homocysteine and methylmalonic acid, at study entry, in a large multivariate analysis, suggesting that such toxicity and possibly some deaths may be related to reduced folic acid and vitamin B_{12} pools.[29] Therefore, beginning December 2, 1999, folic acid and vitamin B_{12} supplementation was required for all patients receiving pemetrexed and for those subsequently enrolled in this study. This change resulted in three patient subgroups that were defined by supplementation status: (1) never supplemented patients (NS) completed treatment before the protocol change (ie, December 2, 1999); (2) partially supplemented patients (PS) began treatment before this date and completed treatment after that date; (3) fully supplemented patients (FS) began treatment after that date. To ensure adequate statistical power of the FS subgroup, the sample size was substantially increased (see statistical plan that appears later).

Treatment

Pemetrexed was administered intravenously (IV) at 500 mg/m^2 over 10 minutes, followed 30 minutes later by cisplatin 75 mg/m^2 IV over 2 hours on day 1 of a 21-day cycle. Patients assigned to the cisplatin arm were treated likewise, except normal saline was given in the place of pemetrexed at equivalent volume. Folic acid 350 to 1,000 μg was taken orally daily beginning 1 to 3 weeks before the first chemotherapy doses and was continued throughout study therapy. Vitamin B_{12} 1,000 μg was given intramuscularly 1 to 3 weeks before the first dose of study therapy and repeated every 9 weeks while a patient was receiving study therapy. In addition, dexamethasone was given the day before, day of, and day after pemetrexed dosing to reduce the risk of severe skin rash. Both vitamin supplementation and dexamethasone were given to patients in both arms to maintain patient blinding to study therapy. Other chemotherapy, immunotherapy, or hormonal therapy was not permitted. Supportive care therapies were allowed per protocol during the study.

Dose adjustments for hematologic toxicity were based on a stepwise reduction schedule. Grade 3 or 4 mucositis, diarrhea requiring hospitalization, or grade 3 or 4 nonhematologic effects also resulted in dose reduction for subsequent doses. Any patient requiring three dose reductions was discontinued from the study. Dose delays up to 42 days were permitted for recovery from study drug toxicity. Dose escalations were not allowed.

Assessments During and After Treatment

Baseline and predosing assessment included a complete history and physical examination, complete blood cell count, calculated creatinine clearance, liver enzymes, blood electrolytes, blood albumin, calcium and glucose, and vitamin metabolites. Survival was defined as the time from randomization to the time of death from any cause. Patients who were alive on the date of last follow-up were censored on that date. Time to progressive disease was defined as the time from randomization until documented progression or death from any cause. For patients without progressive disease at the time of analysis, the date of last follow-up was considered right-censored. Duration of tumor response was defined as the time from the first objective status of a response to the time of documented disease progression or death from any cause. Chest imaging was performed at least once just before every other treatment while a patient was receiving study therapy and approximately every 6 weeks after completion of study therapy. Time to treatment failure was defined as the time from randomization to the date of observed disease progression, death from any cause, or early discontinuation of treatment.

Change in disease was assessed by measuring the thickness of up to three involved areas of pleural rind at each of three separate levels at least 2 cm apart on computed tomography scan, at baseline, and every other cycle (at least one measurement was $>$ 1.5 cm).[30] A complete response (CR) was defined as complete absence of measurable, nonmeasurable but assessable, and unassessable disease with no new lesions and no disease-related symptoms. A PR was defined as ≥ 50% reduction from baseline of the sum of the products of perpendicular diameters of bidimensionally measurable disease when only such disease was present, ≥ 30% decrease in the sum of the greatest diameters of unidimensionally measurable lesions when only such disease was present, or reduction of either type of disease as defined above and the other type at least stable when both types were present, with nonmeasurable lesions being at least stable, with no new lesions. Any CR or PR required confirmation 4 weeks later. Tumor response rate was defined as the proportion of patients who experienced either a CR or PR times 100. Tumor progression was defined as the appearance of a new or relapsed lesion/site, a 50% increase in the sum of products of all bidimensionally measurable lesions over the smallest sum observed when only such disease was present, a 25% increase in the sum of the longest dimension of unidimensionally measurable lesions over smallest sum observed when only such disease was present (in the presence of both disease types, progression of either type as defined above and at least stable disease for the other), worsening of assessable disease, or death from disease. Stable disease was disease that did not qualify for CR, PR, or progression.

Statistical Analyses

The primary statistical analysis compared survival times between the two study arms. This primary analysis was conducted on an intent-to-treat (ITT) basis. Secondary analyses were conducted comparing subgroups defined by supplementation status within or across treatment arms to assess the effect of supplementation on safety and efficacy. Unless otherwise noted, all tests of hypotheses were conducted at the alpha = 0.050 level, with a 95% confidence interval.

Kaplan-Meier nonparametric techniques[31] were used for the comparison of survival times between the two treatment arms in the ITT population. Differences were assessed using a two-sided log-rank test. Because an interim analysis was conducted (resulting in a decision to continue the trial

Table 1. Patient Characteristics

	Pemetrexed/Cisplatin				Cisplatin			
	Intent to Treat (n = 226)	Full Supplementation (n = 168)	Partial Supplementation (n = 26)	Never Supplemented (n = 32)	Intent to Treat (n = 222)	Full Supplementation (n = 163)	Partial Supplementation (n = 21)	Never Supplemented (n = 38)
Age, years								
Median	61	60	62.5	61	60	60	62	59.5
Range	29-85	29-85	38-75	32-77	19-84	19-82	36-81	35-84
Sex								
Male								
No. of patients	184	136	22	26	181	134	18	29
%	81.4	81.0	84.6	81.3	81.5	82.2	85.7	76.3
Female								
No. of patients	42	32	4	6	41	29	3	9
%	18.6	19.0	15.4	18.8	18.5	17.8	14.3	23.7
Race								
White								
No. of patients	204	150	23	31	206	153	19	34
%	90.3	89.3	88.5	96.9	92.8	93.9	90.5	89.5
Other*								
No. of patients	22	18	3	1	16	10	2	4
%	9.7	10.7	11.5	3.1	7.2	6.1	9.5	10.5
Performance status								
70								
No. of patients	37	25	3	9	31	22	3	6
%	16.4	14.9	11.5	28.1	14.0	13.5	14.3	15.8
80								
No. of patients	72	58	7	7	66	47	7	12
%	31.9	34.5	26.9	21.9	29.7	28.8	33.3	31.6
90/100								
No. of patients	117	85	16	16	125	94	11	20
%	51.8	50.6	61.5	50.0	56.3	57.7	52.4	52.6
Histology								
Epithelial								
No. of patients	154	117	18	19	152	113	14	25
%	68.1	69.6	69.2	59.4	68.5	69.3	66.7	65.8
Sarcomatoid								
No. of patients	18	14	2	2	25	17	3	5
%	8.0	8.3	7.7	6.3	11.3	10.4	14.3	13.2
Mixed cell								
No. of patients	37	25	4	8	36	25	4	7
%	16.4	14.9	15.4	25.0	16.2	15.3	19.0	18.4
Unspecified								
No. of patients	17	12	2	3	9	8	0	1
%	7.5	7.1	7.7	9.4	4.1	4.9	0.0	2.6
Stage								
I								
No. of patients	16	15	1	0	14	12	0	2
%	7.1	8.9	3.8	0.0	6.3	7.4	0.0	5.3
II								
No. of patients	35	27	5	3	33	27	2	4
%	15.6	16.2	19.2	9.4	15.0	16.8	9.5	10.5
III								
No. of patients	73	51	12	10	68	49	9	10
%	32.4	30.5	46.2	31.3	30.9	30.4	42.9	26.3
IV								
No. of patients	102†	75†	8	19	107†	75†	10	22
%	45.1	44.6	30.8	59.4	48.2	46.0	47.6	57.9

*Includes Hispanics, Asians, and patients of African descent.

†Includes patients with unspecified stage (one patient in pemetrexed/cisplatin arm and two patients in cisplatin arm).

to planned completion), the comparison of survival times was tested at the $\alpha = .0476$ level. To assess the impact of supplementation on survival times in the pemetrexed/cisplatin arm, the Kaplan-Meier analysis of survival time was conducted on FS and on FS + PS patients. Statistical analyses of time-to-event secondary efficacy variables were comparable to those of the primary efficacy variable. Comparisons of the tumor response rates between the two treatment arms was made using the Fisher's exact test with 95% CIs calculated using the method of Leemis and Trivedi.[32] Dose-intensity (DI) was calculated as mean dose in milligrams per square meter per week. The percentage of planned DI delivered was calculated as the mean DI delivered in milligrams per square meter per week divided by the planned DI in milligrams per square meter per week times 100. The incidence of common toxicity criteria toxicities was analyzed using Fisher's exact test.

Table 2. Summary of Study Drug Administration

	Pemetrexed/Cisplatin				Cisplatin			
	Intent to Treat (n = 226)	Full Supplementation (n = 168)	Partial Supplementation (n = 26)	Never Supplemented (n = 32)	Intent to Treat (n = 222)	Full Supplementation (n = 163)	Partial Supplementation (n = 21)	Never Supplemented (n = 38)
Cycles given								
Median	6.0	6.0	6.0	2.0	4.0	4.0	6.0	2.0
Range	1-12	1-12	2-6	1-6	1-9	1-9	2-6	1-6
% Completing at least four cycles	71.2	73.2	96.1	40.6	55.4	55.2	85.7	39.5
% Completing at least six cycles	53.1	57.7	65.4	18.8	40.1	40.5	66.7	23.7
% Completing at least eight cycles	5.3	7.1	0	0	2.3	3.1	0	0
Dose delivered, pemetrexed								
DI, mg/m^2/wk	153.4	154.6	141.3	156.6	N/A	N/A	N/A	N/A
% Planned DI	92.0	92.8	84.8	94.0	N/A	N/A	N/A	N/A
Dose delivered, cisplatin								
DI, mg/m^2/wk	23.2	23.4	21.5	23.5	24.1	24.1	23.9	24.3
% Planned DI	92.8	93.6	86.0	94.0	96.4	96.4	95.6	97.2

Abbreviations: DI, dose-intensity; N/A, not applicable.

RESULTS

Patient Characteristics

From April 1999 to March 2001, 574 patients signed informed consent, and of 456 eligible patients, 226 received pemetrexed/cisplatin, and 222 received cisplatin alone. (Eight randomly assigned patients went off study before receiving any study drug; reasons were patient decision [four patients], inclusion criteria not met [two patients], hypertension [one patient],and death from study disease [one patient]). These 448 patients were assessable for efficacy and toxicity as the ITT population.

As seen in Table 1, treatment arms were well balanced with respect to baseline characteristics. Patients were predominantly male and white, with a median age of 61 years (range, 19 to 85 years). Approximately two thirds of the patients had epithelial histology, whereas 78% had stage III or stage IV disease. The most common metastatic sites included pleural rind, mediastinal lymph node, lung, and chest wall. No patient had prior systemic chemotherapy, but 12% of patients had prior radiotherapy. Pemetrexed/cisplatin patients received more treatment cycles (median, six cycles; range, one to 12 cycles) than those receiving cisplatin alone (median, four cycles; range, one to nine cycles; Table 2). Similarly, within each arm, supplemented patients received more cycles than never-supplemented patients. The delivered DI of study drugs was highly efficient, exceeding 90% in both arms. Median follow-up was 10.0 months.

Efficacy

Survival curves of the ITT population and FS subgroup for each arm are shown in Figure 1A and 1B, respectively. The median survival time for pemetrexed/cisplatin-treated patients was longer than for patients receiving cisplatin alone: 12.1 months versus 9.3 months, representing a highly statistically significant difference (Table 3). In the FS subgroup, median survival time was 13.3 months for the pemetrexed/cisplatin arm and 10.0 months in the control arm, representing a difference that approaches statistical significance ($P = .051$). Although the PS-only subgroup was a relatively small subset, comparison of this subgroup between the two arms showed a hazard ratio of 0.78, which was comparable to that of the FS subgroups. We therefore combined these subgroups to explore the effect of treatment on the subgroup of patients who received supplementation at some time during their therapy (ie, FS/PS). As can be seen in Table 3, the comparison of survival time between the two arms showed a similar treatment effect: 13.2 months for the pemetrexed/cisplatin arm versus 9.4 months for the control arm ($P = .022$). However, in the NS subgroup, there was no statistically significant difference between the two arms; this was likely due at least in part to the small numbers of patients in each subgroup (data not shown).

As with survival duration, the median time to progressive disease was significantly longer for patients who received pemetrexed and cisplatin as compared with patients who received cisplatin alone (5.7 months *v* 3.9 months; $P = .001$; Fig 2A, Table 3). This difference was similar for both the FS and FS/PS subgroups as well (Fig 2B, Table 3). The median time to treatment failure was also significantly longer in the pemetrexed/cisplatin arm than in the control arm. Again, the results were similar in the FS and FS/PS subgroups. The response rates are listed in Table 3. All responses were PRs: 41.3% of pemetrexed/cisplatin patients versus 16.7% in the control group. This magnitude of effect was similar in the vitamin-supplemented subgroups.

Toxicity

Hematologic toxicities are summarized as worst grade 3 or 4 toxicity in Tables 4 and 5. In the control arm, severe toxicity was uncommon. In the pemetrexed/cisplatin arm, grade 3/4 neutropenia (27.9%) and grade 3/4 leukopenia (17.7%) were the most common hematologic toxicities. Toxicity within this arm was analyzed comparing supplementation subgroups in two ways (ie, FS *v* combined PS/NS patients and FS/PS combined *v* NS patients; Table 5). The incidence of grade 3/4 neutropenia was significantly higher among NS/PS patients (41.4%) compared with FS patients (23.3%; $P = .011$); this difference was similar when PS/FS patients were compared with NS patients. A similar but nonsignificant trend was observed for leukopenia: 25.8% for PS/NS patients

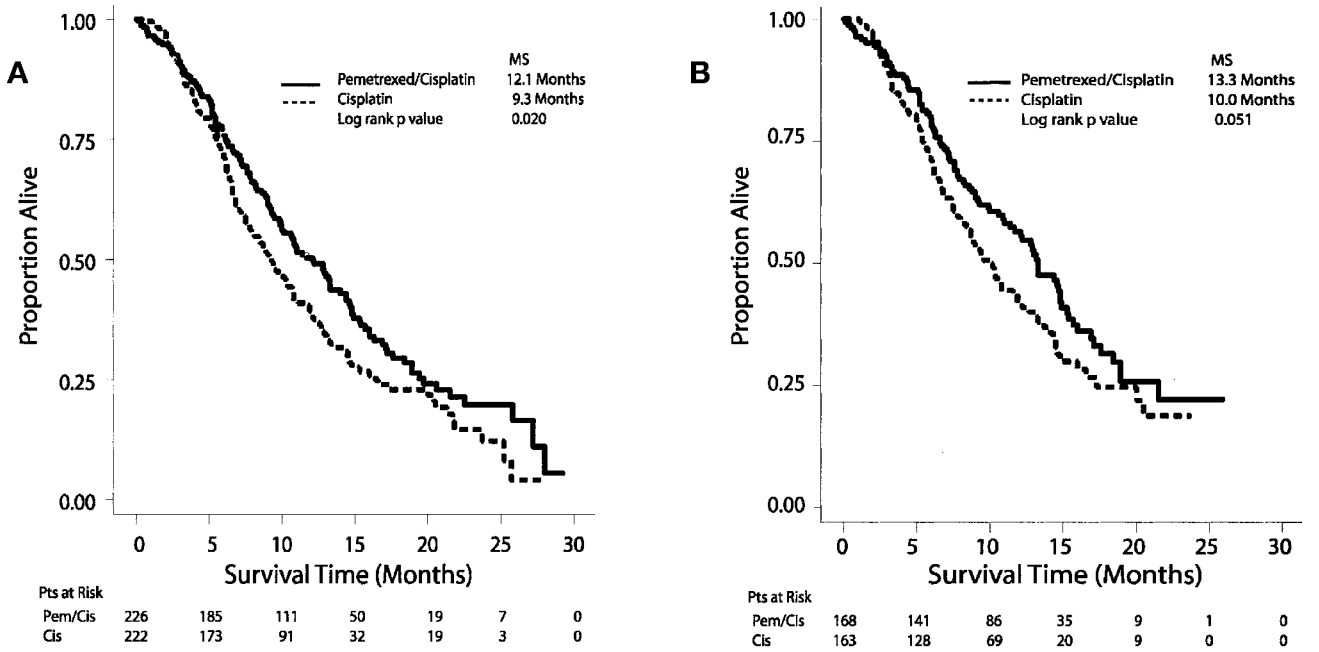

Fig 1. Kaplan-Meier estimates of overall survival time for all patients (Pts) (A) and for fully supplemented patients (B). Overall survival was significantly longer for the pemetrexed/cisplatin-treated patients (Pem/Cis) in the group of all patients ($P = .020$) and approached significance for the group of fully supplemented patients ($P = .051$). MS, median survival; Cis, cisplatin alone.

versus 14.9% for FS patients ($P = .072$). Nonhematologic laboratory toxicity was infrequent, with five episodes of decreased creatinine clearance and three episodes of hyponatremia, all in pemetrexed/cisplatin patients (data not shown).

Clinical toxicities are also listed in Tables 4 and 5. In both treatment groups, nausea, vomiting, and fatigue were the most commonly reported nonlaboratory toxicities, with ≥ 88% of events reported as grade 3. The incidence of nausea, vomiting,

Table 3. Results From Analysis of Efficacy Parameters

	Intent to Treat		Fully Supplemented		Fully and Partially Supplemented	
	Pemetrexed/Cisplatin (n = 226)	Cisplatin (n = 222)	Pemetrexed/Cisplatin (n = 168)	Cisplatin (n = 163)	Pemetrexed/Cisplatin (n = 194)	Cisplatin (n = 184)
Survival						
Median, months	12.1	9.3	13.3	10.0	13.2	9.4
95% CI for median	10.0 to 14.4	7.8 to 10.7	11.4 to 14.9	8.4 to 11.9	10.9 to 14.8	8.4 to 11.6
Hazard ratio	0.77		0.75		0.71	
Log-rank *P*	.020		.051		.022	
Wilcoxon *P*	.028		.039		.019	
1-year survival, %	50.3	38.0	56.5	41.9	54.1	40.9
*P**	.012		.011		.014	
Percent censored	35.8	28.4	43.5	36.8	41.2	33.2
Time to PD						
Median, months	5.7	3.9	6.1	3.9	6.1	4.3
95% CI for median	4.9 to 6.5	2.8 to 4.4	5.3 to 7.0	2.8 to 4.5	5.4 to 6.7	3.0 to 4.9
Hazard ratio	0.68		0.64		0.70	
Log-rank *P*	.001		.008		.003	
Wilcoxon *P*	< .001		< .001		< .001	
Percent censored	7.5	9.0	8.9	12.3	8.8	10.9
Tumor response†						
Response rate, %	41.3	16.7	45.5	19.6	45.6	19.0
95% CI for response rate	34.8 to 48.1	12.0 to 22.2	37.8 to 53.4	13.8 to 26.6	38.4 to 52.9	13.6 to 25.4
Fisher's exact *P*	< .001		< .001		< .001	

Abbreviation: CI, confidence interval; PD, progressive disease.

*Two-sided *P* value based on standard normal distribution.

†One pemetrexed/cisplatin patient did not have measurable disease at baseline and was excluded from analysis of tumor response rate.

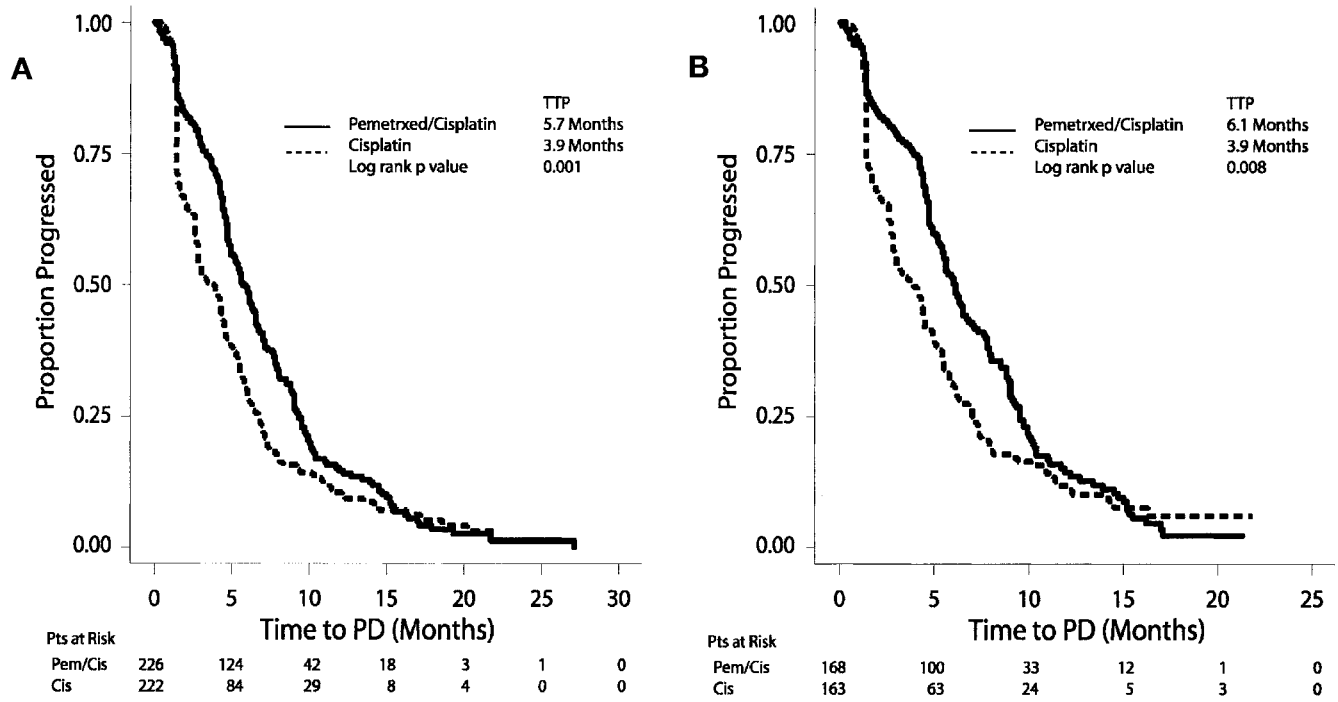

Fig 2. Kaplan-Meier estimates of time to progressive disease (PD) for all patients (Pts) (A) and for fully supplemented patients (B). Time to progressive disease was significantly longer for pemetrexed/cisplatin-treated patients (Pem/Cis) in the group of all patients ($P = .001$) and in the group of fully supplemented patients ($P = .008$). TTP, time to progression; Cis, cisplatin alone.

fatigue, diarrhea, dehydration, and stomatitis were significantly higher in the pemetrexed/cisplatin arm. In the pemetrexed/cisplatin arm, the FS subgroup experienced consistently less toxicity (except for dehydration), including less than a 1% incidence of febrile neutropenia. The FS/PS subgroup showed a similar reduction in toxicity, with differences in nausea, vomiting, and febrile neutropenia reaching statistical significance.

Fourteen patients receiving pemetrexed/cisplatin died while on study therapy or within 30 days of the last dose of study drug, compared with eight patients receiving cisplatin alone (6.2% *v* 3.6%). Three deaths thought to be at least possibly study drug-related occurred in the pemetrexed/cisplatin arm before adding vitamin supplementation; none occurred thereafter. The remaining deaths were thought to be disease-related.

DISCUSSION

This multicenter phase III study demonstrated a statistically significant improvement in survival time in MPM patients treated

Table 4. Summary of Maximum Common Toxicity Criteria Grade 3/4 Toxicities

	Pemetrexed/Cisplatin, Intent to Treat (n = 226)		Cisplatin, Intent to Treat (n = 222)		
	No. of Patients	%	No. of Patients	%	*P*
Hematologic laboratory toxicity					
Hemoglobin	11	4.8	0	0	.001
Leukocytes	40	17.7	2	0.9	< .001
Neutrophils	63	27.9	5	2.3	< .001
Platelets	13	5.8	0	0	< .001
Nonlaboratory toxicity					
Nausea	33	14.6	14	6.3	.005
Fatigue	23	10.2	19	8.6	.628
Vomiting	30	13.3	8	3.6	.000
Diarrhea	10	4.4	0	0	.002
Dehydration	9	4.0	1	0.5	.020
Stomatitis	9	4.0	0	0	.004
Anorexia	5	2.2	1	0.5	.216
Febrile neutropenia	4	1.8	0	0	.123
Infection with G3 or G4 neutropenia	3	1.3	1	0.5	.623
Rash	3	1.3	0	0	.248

*Fisher's exact *P* value for comparison of intent-to-treat pemetrexed and cisplatin group versus intent-to-treat cisplatin group.

Table 5. Summary of Maximum Common Toxicity Criteria Grade 3/4 Toxicities From Pemetrexed/Cisplatin-Treated Patients

	Full Supplementation (n = 168)		Partial Supplementation + Never Supplemented (n = 58)			Full Supplementation + Partial Supplementation (n = 194)		Never Supplemented (n = 32)		
	No. of Patients	%	No. of Patients	%	P*	No. of Patients	%	No. of Patients	%	P*
Hematologic Laboratory Toxicity										
Hemoglobin	7	4.2	4	6.9	.479	8	4.1	3	9.4	.192
Leukocytes	25	14.9	15	25.9	.072	29	14.9	11	34.4	.012
Neutrophils	39	23.2	24	41.4	.011	51	26.3	12	37.5	.205
Platelets	9	5.4	4	6.9	.744	10	5.2	3	9.4	.403
Nonlaboratory Toxicity										
Nausea	20	11.9	13	22.4	.082	23	11.9	10	31.3	.012
Fatigue	17	10.1	6	10.3	.999	18	9.3	5	15.6	.338
Vomiting	18	10.7	12	20.7	.071	20	10.3	10	31.3	.003
Diarrhea	6	3.6	4	6.9	.284	7	3.6	3	9.4	.154
Dehydration	7	4.2	2	3.4	.999	7	3.6	2	6.3	.619
Stomatitis	5	3.0	4	6.9	.240	8	4.1	1	3.1	.999
Anorexia	2	1.2	3	5.2	.108	3	1.5	2	6.3	.148
Febrile neutropenia	1	0.6	3	5.2	.053	1	0.5	3	9.4	.009
Infection with G3 or G4 neutropenia	0	0	3	5.2	.016	1	0.5	2	6.3	.053
Rash	1	0.6	2	3.4	.163	3	1.5	0	0.0	.999

*Fisher's exact *P* value for within–pemetrexed/cisplatin arm comparisons for the full supplementation versus partial supplementation plus never supplemented subgroups and for the full supplementation plus partial supplementation versus never supplemented subgroups.

with pemetrexed/cisplatin compared with cisplatin alone. This improvement is also clinically relevant; the additional survival time of 2.8 months in the pemetrexed/cisplatin arm is nearly twice as long as the 6-week median survival improvement found in meta-analyses and used to justify recommendations for the use of cisplatin-containing regimens in advanced non–small-cell lung cancer.[33,34] The 2.8-month survival benefit represents a hazard ratio of 0.77 or relative risk reduction for death of 23%. A risk reduction of this magnitude is usually considered a meaningful incremental survival-time improvement in oncology trials. Design features such as the large sample size and multiple strata of prognostic factors in the randomization scheme gives added confidence that this result is robust, generalized, and attributable mainly, if not solely, to the addition of pemetrexed to the treatment regimen. In addition, the presence of a high percentage of patients with advanced disease stage (III/IV) and a median survival time in the control arm that exceeded literature-based expectations,[4,5] adds to the credibility of the results. Data from two other randomized MPM trials have been reported. Samson et al reported the results of a randomized intergroup trial of cyclophosphamide, imidazole carboxamide, and doxorubicin versus cyclophosphamide and doxorubicin.[17] The sample size was underpowered (n = 76), but there was no significant difference in survival or duration of response. A second randomized trial of ranpirnase versus doxorubicin was recently reported as an abstract.[19] That trial enrolled 154 patients, and the median survival time was not significantly different in the two arms (7.7 months in the ranpirnase group and 8.2 months in the doxorubicin group).

Other antifolates (trimetrexate [response rate, 12%],[35] edatrexate [response rate, 18% and 25%],[36] and methotrexate [response rate, 37%][37]) have been tested in single-agent, phase II studies of patients with MPM. Although these studies suggest that other antifolate drugs may have some activity against pleural mesothelioma, they have not been tested in randomized trials as single agents or combinations against appropriate contemporaneous control groups. As such, the evidence supporting the use of other antifolates, in practice, remains weak. Interestingly, antitumor activity may be mediated through a newly identified class of high affinity alpha-folate receptors found on mesothelioma cells of all histologic subtypes.[38]

In addition to examining MPM treatment regimens, this study also looked at the effect of vitamin supplementation on those regimens. Patients receiving pemetrexed/cisplatin with vitamins had greater improvement in all efficacy parameters than those receiving the same regimen without vitamins. Surprisingly, patients receiving cisplatin alone also seemed to benefit from the vitamin supplementation, though to a lesser degree. Supplementation enabled patients to receive more cycles of treatment (Table 2), and this may explain these results. Most importantly, there was no adverse effect of vitamin supplementation on efficacy because the results of survival and other time-to-event outcomes consistently favored the pemetrexed/cisplatin therapy.

The overall toxicity and response profile of pemetrexed/cisplatin seemed to be similar to or better than that reported with other two-drug chemotherapeutic regimens studied in patients with MPM. However, a phase III study comparing this regimen to another widely used regimen, such as gemcitabine/cisplatin[10,11] would be necessary to clarify that hypothesis. The primary toxicity profile of pemetrexed (mucositis, neutropenia, and leukopenia) does not overlap that of cisplatin (gastrointestinal, neurological, and renal), thus supporting their use in combination. Patients who received vitamin supplementation had a notable reduction in hematologic toxicity, specifically grade 3/4 neutropenia and leukopenia, an improvement in clinical toxicity. Overall improvement in severe toxicity has been observed in other pemetrexed studies because vitamin supplementation became a standard of pemetrexed therapy.[29]

This study had some limitations. Although crossover of control patients to pemetrexed was not permitted, second-line therapy was not controlled in this trial. As a result, 37.6% of

patients on the pemetrexed/cisplatin arm and 47.3% on the control arm received second-line chemotherapy. Despite the potential risk for survival to be preferentially extended in the control arm because of its higher frequency of second-line therapy, the observed treatment effect remained statistically and clinically significant in favor of pemetrexed/cisplatin. End points, such as time to progressive disease and time to treatment failure, are unlikely to be influenced by second-line treatment, yet these outcomes were also significantly improved by pemetrexed/cisplatin. Another limitation was the lack of a double-blind design, because outcome measurements of response and time to progression could be biased by prior investigator knowledge of the treatment assignment. The response rates for both arms were as good or better than those published in most other single-agent and combination phase II studies, a result possibly influenced by such a bias or by the measurement method used in this study.

In conclusion, pemetrexed/cisplatin therapy was associated with significantly improved survival time and with overall greater antitumor activity compared with cisplatin alone. The regimen was well tolerated, particularly in patients who received low-dose folic acid and vitamin B_{12}. Vitamin supplementation reduced toxicity with no apparent adverse affect on efficacy.

ACKNOWLEDGMENT

We thank Shanti Pruitt, Sheila Swain, Mary Dugan, and Patrick McAndrews for their assistance in conducting the study or preparing this manuscript.

APPENDIX

The appendix is included in the full text version of this article only, available on-line at www.jco.org. It is not included in the PDF version.

REFERENCES

1. Sugarbaker DJ, Garcia JP, Richards WG, et al: Extrapleural pneumonectomy in the multimodality therapy of malignant pleural mesothelioma: Results in 120 consecutive patients. Ann Surg 224:288-296, 1996

2. Rusch VW, Venkatraman ES: Important prognostic factors in patients with malignant pleural mesothelioma, managed surgically. Ann Thorac Surg 68:1799-1804, 1999

3. Boutin C, Schlesser M, Freneay C, et al: Malignant pleural mesothelioma. Eur Respir J 12:972-981, 1998

4. Ruffie PA: Pleural mesothelioma. Curr Opin Oncol 3:328-334, 1991

5. DePangher-Manzini V, Brollo A, Franceschi S, et al: Prognostic factors of malignant mesothelioma of the pleura. Cancer 72:410-417, 1993

6. Herndon JE, Green MR, Chahinian AP, et al: Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the cancer and Leukemia Group B. Chest 113:723-731, 1998

7. Law MR, Gregor A, Hodson ME, et al: Malignant mesothelioma of the pleura: A study of 52 treated and 64 untreated patients. Thorax 39:255-259, 1984

8. Sterman DH, Kaiser LR, Albelda SM: Advances in the treatment of malignant pleural mesothelioma. Chest 116:504-520, 1999

9. Ryan CW, Herndon J, Vogelzang NJ: A review of chemotherapy trials for malignant mesothelioma. Chest 113:66S-73S, 1998 (suppl 1)

10. Byrne MJ, Davidson JA, Musk AW, et al: Cisplatin and gemcitabine treatment for malignant mesothelioma: A phase II study. J Clin Oncol 17:25-30, 1999

11. van Haarst JM, Baas P, Manegold CH, et al: Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. Br J Cancer 86:342-345, 2002

12. Kindler HL, Millard F, Herndon JE 2nd, et al: Gemcitabine for malignant mesothelioma: A phase II trial by the Cancer and Leukemia Group B. Lung Cancer 31:311-331, 2001

13. White SC, Anderson H, Jayson GC, et al: Randomised phase II study of cisplatin-etoposide versus infusional carboplatin in advanced non-small-cell lung cancer and mesothelioma. Ann Oncol 11:201-206, 2000

14. van Meerbeeck JP, Baas P, Debruyne C, et al: A phase II study of gemcitabine in patients with malignant pleural mesothelioma: European Organization for Research and Treatment of Cancer, Lung Cancer Cooperative Group. Cancer 85:2577-2582, 1999

15. Fizazi K, Caliandro R, Soulie P, et al: Combination raltitrexed (Tomudex) oxaliplatin: A step forward in the struggle against mesothelioma? The Institut Gustave Roussy experience with chemotherapy and chemo-immunotherapy in mesothelioma. Eur J Cancer 36:1514-1521, 2000

16. Sorensen PG, Bach F, Bork E, et al: Randomized trial of doxorubicin versus cyclophosphamide in diffuse malignant pleural mesothelioma. Cancer Treat Rep 69:1431-1432, 1985

17. Samson MK, Wasser LP, Borden EC, et al: Randomized comparison of cyclophosphamide, imidazole carboxamide, and adriamycin versus cyclophosphamide and adriamycin in patients with advanced stage malignant mesothelioma: A Sarcoma Intergroup study. J Clin Oncol 5:86-91, 1987

18. Chahinian AP, Antman K, Goutsou M, et al: Randomized phase II trial of cisplatin with mitomycin or doxorubicin for malignant mesothelioma by the Cancer and Leukemia Group B. J Clin Oncol 11:1559-1565, 1993

19. Vogelzang N, Taub R, Shin D, et al: Phase III randomized trial of onconase (Onc) vs. doxorubicin (Dox) in patients (pts) with unresectable malignant mesothelioma (UMM): Analysis of survival. Proc Am Soc Clin Oncol 19:577, 2000 (abstr 2274)

20. Taylor EC: Design and synthesis of inhibitors of folate-dependent enzymes as antitumor agents. Adv Exp Med Biol 338:387-408, 1993

21. Shin DM, Scagliotti GV, Kindler HL, et al: A phase II trial of pemetrexed in malignant pleural mesothelioma (MPM) patients: Clinical outcome, role of vitamin supplementation, respiratory symptoms and lung function. Proc Am Soc Clin Oncol 21:294, 2002 (abstr 1175)

22. Schultz RM, Chen VJ, Bewley JR, et al: Biological activity of the multitargeted antifolate, MTA (LY231514), in human cell lines with different resistance mechanisms to antifolate drugs. Semin Oncol 26:68-73, 1999 (suppl 6)

23. Mendelsohn LG, Shih C, Chen VJ, et al: Enzyme inhibition, polyglutamation, and the effect of LY231514 (MTA) on purine biosynthesis. Semin Oncol 26:42-47, 1999 (suppl 6)

24. Moran RG: Roles of folylpoly-gamma glutamate synthetase in therapeutics with tetrahydrofolate antimetabolites: An overview. Semin Oncol 26:24-32, 1999 (suppl 6)

25. Shih C, Chen VJ, Gossett LS, et al: LY231514, a pyrrolo [2, 3-d] pyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. Cancer Res 57:1116-1123, 1997

26. Thodtmann R, Depenbrock H, Dumez H, et al: Clinical and pharmacokinetic phase I study of multitargeted antifolate (LY231514) in combination with cisplatin. J Clin Oncol 17:3009-3016, 1999

27. Calvert AH, Hughes AN, Calvert PM, et al: ALIMTA in combination with carboplatin demonstrates clinical activity against malignant mesothelioma in a phase I trial. Lung Cancer 29:73-74, 2000 (suppl 2)

28. Shepherd FA, Dancey J, Arnold A, et al: Phase II study of pemetrexed in patients with advanced nonsmall cell lung cancer. Cancer 92:595-600, 2001

29. Niyikiza C, Baker SD, Seitz DE, et al: Homocysteine and methylmalonic acid: Markers to predict and avoid toxicity from pemetrexed therapy. Mol Cancer Ther 1:545-552, 2002

30. Nowak AK, Byrne MJ: Assessment of response in malignant mesothelioma (MM). Proc Am Soc Clin Oncol 479a:1848, 1999 (abstr)

31. Kaplan EL, Meier P: Nonparametric estimation of incomplete observations. J Am Stat Assoc 53:457-481, 1958

32. Leemis LM, Trivedi KS: A comparison of approximate interval estimators for the Bernoulli Parameter. Am Stat 50:63-68, 1996

33. Non-Small Cell Lung Cancer Collaborative Group: Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomized clinical trials. BMJ 311:899-909, 1995

34. Clinical practice guidelines for the treatment of unresectable non-small cell lung cancer: Adopted on May 16, 1997 by the American Society of Clinical Oncology. J Clin Oncol 15:2996-3018, 1997

35. Vogelzang NJ, Weissman LB, Herndon JE, et al: Trimetrexate in malignant mesothelioma: A CALGB phase II study. J Clin Oncol 12:1436-1442, 1994

36. Kindler HL, Belani C, Herndon JE, et al: Edatrexate (10-ethyl-deaza-aminopterin) (NSC #626715) with or without leucovorin rescue for malignant mesothelioma: Sequential phase II trials by the Cancer and Leukemia Group B. Cancer 86:1985-1991, 1999

37. Solheim OP, Saeter G, Finnanger AM, et al: High-dose methotrexate in the treatment of malignant mesothelioma of the pleura: A phase II study. Br J Cancer 65:956-960, 1992

38. Wang Y, Zhao R, Chattopadhyay S, et al: A novel folate transport activity in human mesothelioma cell lines with high affinity and specificity for the new-generation antifolate, pemetrexed. Cancer Res 62:6434-6437, 2002