Single-Agent Pemetrexed for Chemonaïve and Pretreated Patients with Malignant Pleural Mesothelioma

Results of an International Expanded Access Program

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Introduction: Pemetrexed has established efficacy, and is the backbone for chemotherapy in patients with malignant pleural mesothelioma (MPM). An International Expanded Access Program provided >3000 mesothelioma patients with access to single-agent pemetrexed or pemetrexed plus platinum analogs (cisplatin or carboplatin) in 13 countries. In this article, we report the safety and efficacy data of MPM patients who were treated with single-agent pemetrexed (n = 812).

Methods: Patients with histologically confirmed MPM, not amenable to curative surgery, received pemetrexed (500 mg/m^2) once (day 1) every 21 days with standard premedication and vitamin supplementation. Investigator-determined response and survival data were recorded at the end of study participation. Myelosuppression data were also collected.

Results: All 812 MPM patients (319 chemonaïve; 493 pretreated) received single-agent pemetrexed (≥1 dose) and were evaluated for safety. A total of 643 patients (247 chemonaïve, 396 pretreated) were evaluated for efficacy. Of the chemonaïve patients evaluated for efficacy (n = 247), the overall response rate was 10.5%, median time to progressive disease (TTPD) was 6.0 months, and median survival was 14.1 month. Of the pretreated patients evaluated for efficacy (n = 396), the overall response rate was 12.1%, median TTPD was 4.9 months, and the median survival was not estimable due to high censoring. Common terminology criteria grade 3/4 hematologic toxicity was mild in both groups, with neutropenia (<18%) as the main toxicity.

Conclusions: In the present expanded access program, single-agent pemetrexed demonstrated promising activity in MPM in both chemonaïve and pretreated patients, with TTPD of 6.0 and 4.9 months, respectively, 1-year survival ≥54.7%, and mild hematologic toxicity.

Key Words: Chemonaïve, Expanded access program, Malignant pleural mesothelioma, Pemetrexed, Pretreated patients.

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Malignant pleural mesothelioma (MPM) is a rapidly progressive malignancy, with a median survival shorter than 1 year,[1] that is typically associated with prior exposure to asbestos.[2] Although a number of chemotherapy regimens have been evaluated in the past 2 decades, no single-agent treatments have been associated with prolonged survival.[3–6]

Anthracyclines, cisplatin, carboplatin, mitomycin, and ifosfamide were evaluated extensively in phase II trials, in which response rates varying from 14 to 24% and survival times shorter than 1 year were reported.[3] Ellis et al. conducted a systematic review of chemotherapy in patients with advanced MPM[5] and concluded that the pooled overall response rate for single-agent treatment and nonplatinum combination treatment was less than 10% and less than 12%, respectively. Platinum-based combinations were more active, with an overall response rate of approximately 25%.

Antifolates such as raltitrexed, trimetrexate, edatrexate, and methotrexate have been evaluated in single-agent phase II studies of patients with MPM. Although these antifolates demonstrated activity against MPM, evidence supporting their use in clinical practice remains uncertain.[7–10] Combination chemotherapy of raltitrexed plus cisplatin was superior to single-agent cisplatin in a randomized trial.[11]

Pemetrexed is a multitargeted antifolate agent that inhibits multiple enzymes in the folate pathway and has broad antitumor activity in multiple tumor types, including MPM.[12,13] Single-agent pemetrexed received regulatory approval as second-line treatment in advanced nonsmall cell lung cancer,[14] and a phase II trial of single-agent pemetrexed as front-line therapy for MPM showed an overall response rate of 14.1% and a median survival of 10.7 months.[13] Higher response rates with improved survival were seen in MPM patients when pemetrexed was combined with platinum analogs.[15,16] A randomized phase III study of pemetrexed plus cisplatin versus cisplatin in chemonaïve patients with MPM showed a response rate of 41.3 versus 16.7% and a median survival of 12.1 versus 9.3 months, in favor of the combination arm.[17] On the basis of the high response rate and the improvement in overall survival, pemetrexed in combination with cisplatin was approved by the United States Food and Drug Administration in February 2004 for the treatment of patients with MPM who had unresectable disease or who were not candidates for curative surgery.[18] Similar approvals were also granted by European regulatory agencies.

Although the randomized study demonstrated promising results for pemetrexed plus cisplatin,[17] many patients may not be eligible for platinum-containing regimens because of comorbidities, age, and performance status. For this group of patients, single-agent pemetrexed may be a preferrable option.

To further extend the clinical benefit of pemetrexed in patients with mesothelioma, an international Expanded Access Program (EAP) provided patients in 13 European countries with access to pemetrexed (either as pemetrexed-platinum combination therapy or as single-agent therapy) before its commercial availability. The primary objective was to provide patients access to pemetrexed, and the secondary objectives included basic safety data collection, determination of overall best tumor response, and determination of time to progressive disease (TTPD). This report presents results for MPM patients (both chemonaïve and pretreated) who received treatment with single-agent pemetrexed in the EAP. The subset of patients who received pemetrexed in combination with either cisplatin or carboplatin appears to differ in terms of comorbidities, age, and performance status and was therefore not included in the present analysis. Key results for the other patient subgroups were presented previously.[19,20]

PATIENTS AND METHODS

Patients

Patients with a histologically proven diagnosis of mesothelioma who were at least 18-year-old and were not candidates for curative surgery were enrolled in this EAP. Patients were clinically staged using the International Mesothelioma Interest Group Tumor Nodes Metastasis staging criteria.[21] Measurable lesions were not required for enrollment. Patients could have been chemonaïve or may have received one or more lines of prior chemotherapy for malignant mesothelioma. Patients who had prior treatment with pemetrexed were eligible if they had a tumor response or received a clinical benefit from prior pemetrexed treatment. Patients were required to have a performance status $\geq$70 on the Karnofsky scale (KPS) (after any palliative measure, including pleural drainage, had occurred). Patients were required to have adequate bone marrow reserve (absolute neutrophil count [ANC] $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and hemoglobin $\geq$9 g/dL), adequate hepatic function (bilirubin $\leq$1.5 times the upper limit of normal [$\times$ULN], alkaline phosphatase, aspartate transaminase, and alanine transaminase $\leq 3.0\times$ ULN or alkaline phosphatase, aspartate transaminase, and alanine transaminase $\leq 5\times$ ULN if liver had tumor involvement), and adequate renal function (calculated creatinine clearance $\geq$45 mL/min) based on the standard Cockroft and Gault formula.[22] Patients with adequately treated and stable brain metastases not requiring corticosteroid therapy were allowed. Prior pleurodesis was allowed. Pregnant women were not eligible, and all men and women of reproductive potential were required to use an approved method of birth control. Patients with active infection were excluded. Patients with serious concomitant disorders incompatible with the study were excluded at the investigator's decision. Institutional ethical review boards approved the protocol and the study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent before treatment.

Treatment Plan

In this International EAP, patients were assigned to one of the following three options: pemetrexed plus cisplatin, pemetrexed plus carboplatin, or single-agent pemetrexed. The primary treatment option for patients in this EAP was pemetrexed plus cisplatin, but patients who could not tolerate the cisplatin-based regimen were offered one of the other two treatment options. Treatment allocation was done by individual investigators who considered the clinical status of each patient. This report presents the results for patients with MPM who received single-agent pemetrexed.

Pemetrexed 500 mg/m^2 was administered intravenously over 10 minutes on day 1 of a 21-day cycle. Folic acid supplementation, 350 μg to 600 μg or equivalent, was given orally daily beginning approximately 1 to 2 weeks before the first dose of pemetrexed and continuing daily until at least 3 weeks after the last pemetrexed dose. A vitamin B_{12} injection, 1000 μg, was administered intramuscularly approximately 1 to 2 weeks before the first dose of pemetrexed and was repeated approximately every 9 weeks until the patient was discontinued from the study therapy. In addition, dexamethasone 4 mg (or an equivalent corticosteroid) was given orally twice per day on the day before, the day of, and the day after each dose of pemetrexed to reduce the risk of severe skin rash. Study therapy was allowed to continue until there was evidence of progressive disease or until the patient experienced unacceptable toxicity, the investigator decided to

discontinue the patient, the patient requested discontinuation, or if Lilly decided to stop the EAP when pemetrexed became commercially available.

Dose Adjustments

Dose adjustments at the start of a subsequent cycle of therapy were based on platelet and neutrophil nadir (lowest value) counts from the preceding cycle of therapy (ANC had to be $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L before the start of any cycle). Dose delays up to 42 days were permitted for recovery from study-drug toxicity. Upon recovery, the treatment was resumed from the preceding cycle of therapy at 100% of the previous dose for an ANC $\geq 0.5 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L, at 75% of the previous dose for an ANC $< 0.5 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L, or at 50% of the previous dose for platelets $< 50 \times 10^9$/L. Any patient requiring 3 dose reductions was discontinued from the study. In the event of diarrhea requiring hospitalization (or at least grade 3), treatment was delayed until diarrhea had resolved before proceeding. Treatment was then resumed at 75% of the previous dose level. For other nonhematologic events greater than or equal to grade 3 (with the exception of grade 3 transaminase elevation), treatment was delayed until resolution to less than or equal to the patient's baseline grade before proceeding. Treatment was then resumed at 75% of the previous dose level if deemed appropriate by the treating physician.

Efficacy Assessments

Patients' tumor response was assessed preferably using Response Evaluation in Solid Tumors (RECIST) criteria[23]; however, Southwest Oncology Group criteria or World Health Organization criteria were also acceptable for response evaluation. The best overall response rate was determined when the patient completed or was discontinued from the study. The overall tumor response rate was defined as the number of patients with documented partial response or complete response divided by the number of patients qualified for tumor response analysis (evaluable patients). TTPD was estimated in months from the date of the first dose to the date of the first documentation of progressive disease. Survival time was estimated in months from the date of the first dose to the date of death. Survival status was recorded when the patient completed therapy and at one follow-up visit 30 days after study completion.

Safety Assessments

Safety was assessed by physical examination and clinical laboratory tests. Patients were rated for adverse events before each cycle using the Common Terminology Criteria for Adverse Events (CTCAE) scale, version 2. Serious adverse events (SAEs) were required to be reported immediately by the investigators, and were monitored by the Eli Lilly clinical research physician.

Statistical Methods

Summaries of statistics were provided. Missing data were not considered in the efficacy or safety analysis. Only the available data in each cycle were summarized. The investigator-assessed overall best tumor response was summarized with proportion and 95% confidence intervals (CIs). TTPD and survival time were calculated using Kaplan-Meier estimates. Patients for whom no follow-up observation was available were censored. The log-rank test was conducted to compare the chemonaïve and the pretreated patient groups.

All subjects who received at least one dose of the study drug were classified as the safety population. All patients who were in the safety population and who had at least one tumor response observation after baseline were classified as the evaluable efficacy population.

RESULTS

Patient Characteristics and Disposition

A total of 3142 patients with MPM were enrolled at 235 study centers in 13 countries; 2074 patients were chemonaïve and 1011 were pretreated (Figure 1). This manuscript describes the findings in a total of 812 patients with MPM who received treatment with single-agent pemetrexed. Results for other patient subgroups have been described previously.[19,20] Detailed results for chemonaïve patients who received pemetrexed and platinum combinations therapy will also be described in a separate publication.

All 812 patients (319 chemonaïve and 493 pretreated) received at least one dose of single-agent pemetrexed and constituted the safety population. Tumor response data were available for 247 chemonaïve patients and for 396 pretreated patients.

Table 1 presents the baseline demographics and patient characteristics. In both groups, the majority of patients were male ($\geq$75.9%) and Caucasian ($\geq$99.4%). The median age of patients in the chemonaïve and pretreated group was 69 years and 63 years, respectively. The majority of patients had a KPS of 80 or higher (71.6% in the chemonaïve group and 74.5% in the pretreated group). Four patients (1.4%) in the chemonaïve group had a KPS $<$70 and 3 patients (0.6%) in the pretreated group had a KPS $<$70; these 7 patients were in violation of the eligibility criteria requirements.

The main reasons for treatment discontinuation in both of the study groups were objective tumor progression (25.4% in chemonaïve patients, 29.6% in pretreated patients), clinical disease progression (16.6% in chemonaïve patients, 13.2% in pretreated patients), and patient-physician decision (13.5% in chemonaïve patients, 14.4% in pretreated patients). Sixty three patients (24 chemonaïve [7.5%] and 39 pretreated [7.9%]) discontinued because of death from study disease.

Treatment

A median of 4 cycles (range, 1–18 cycles) was administered to the patients in the chemonaïve group; similarly, a median of 4 cycles (range, 1–23 cycles) was administered to the patients in the pretreated group. In the chemonaïve group, 126 patients (39.5%) received 6 cycles and 15 patients (4.7%) received 12 treatment cycles. Similarly, in the pretreated group, 186 patients (37.7%) received 6 cycles and 16 patients (3.2%) received 12 cycles. The relative dose intensity of pemetrexed (i.e., the percentage of dose delivered compared with the planned dose) was 98.3% in the chemonaïve group and 97.9% in the pretreated group.

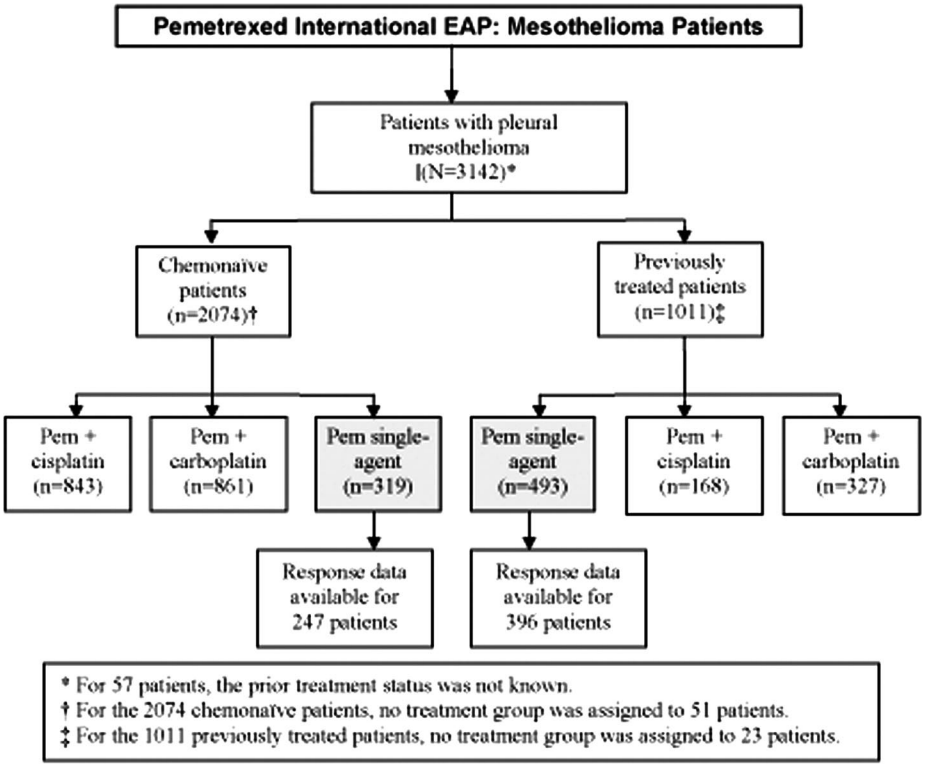

FIGURE 1. MPM patients who enrolled in the pemetrexed International Expanded Access Program. Abbreviations: EAP, expanded access program; N, sample size; n, number of subjects; Pem, pemetrexed. Note: the highlighted boxes are the patient population described in this manuscript.

TABLE 1. Baseline Demographics and Patient Characteristics

Characteristic	Chemonaïve Patients (n = 319)	Pretreated Patients (n = 493)
Median age, yrs (range)	69.0 (39.0–87.0)	63.0 (31.0–85.0)
Gender, *n* (%)		
Male	249 (78.1)	374 (75.9)
Female	70 (21.9)	119 (24.1)
Ethnic origin, *n* (%)		
Caucasian	317 (99.4)	491 (99.6)
African descent	2 (0.6)	0
East/southeast	0	1 (0.2)
Other	0	1 (0.2)
Histological diagnosis, *n* (%)		
Epithelial	195 (61.1)	351 (71.2)
Sarcomatoid	23 (7.2)	16 (3.2)
Mixed cells	19 (6.0)	28 (5.7)
Others	82 (25.7)	98 (19.9)
KPS[a], *n* (%)		
100	42 (14.2)	84 (17.9)
90	57 (19.3)	119 (25.3)
80	113 (38.2)	147 (31.3)
70	80 (27.0)	117 (24.9)
<70	4 (1.4)	3 (0.6)

[a] KPS data available for 296 chemonaïve patients and 470 pretreated patients.
n, number of patients; KPS, Karnofsky performance status.

Efficacy

Of the chemonaïve patients assessable for response (n = 247), 1 (0.4%) had a complete response and 25 (10.1%) patients had a partial response, resulting in an overall response rate of 10.5% (Table 2). An additional 120 patients (48.6%) had stable disease as their best tumor response and 86 (34.8%) had progressive disease. Of the pretreated patients assessable for response (n = 396), none had complete response and 48 (12.1%) patients had a partial response, resulting in an overall response rate of 12.1%. An additional 182 patients (46.0%) had stable disease as their best tumor response and 147 (37.1%) had progressive disease (Table 2).

TABLE 2. Best Overall Response Rate (Evaluable Patients Only)

Response	Chemonaïve Patients (n = 247)	Pretreated Patients (n = 396)
Complete response, *n* (%)	1 (0.4)	0 (0.0)
Partial response, *n* (%)	25 (10.1)	48 (12.1)
Stable disease, *n* (%)	120 (48.6)	182 (46.0)
Progressive disease, *n* (%)	86 (34.8)	147 (37.1)
Unknown, *n* (%)	15 (6.1)	19 (4.8)
Overall response rate, %	10.5	12.1
(95% CI)	(7.0–15.0)	(9.1–15.7)
Disease control rate (responder + stable disease), %	59.1	58.1
(95% CI)	(52.7, 65.3)	(53.0, 63.0)

n, number of patients; CI, confidence interval.

TABLE 3. Time to Progressive Disease and Survival Results in Efficacy Evaluable Population

Event	Chemonaïve Patients (n = 247)	Pretreated Patients (n = 396)
Median TTPD, mo	6.0	4.9
(95% CI)	(4.6, 7.2)	(4.2, 5.8)
Median survival, mo	14.1	NE
(95% CI)	(10.4, 16.4)	(8.8, NE)
One-year survival rate, %	58.6	54.7
(95% CI)	(43.4, 73.8)	(42.6, 66.8)
Censor rate, %	79.3	78.9

n, number of patients; TTPD, time to progressive disease; CI, confidence interval; NE, not estimable due to the large percent of censored records.

The disease control rate (complete response + partial response + stable disease) for chemonaïve and pretreated patients was 59.1 and 58.1%, respectively.

Results for median TTPD, median survival, and 1-year survival rates for the efficacy evaluable population are presented in Table 3. The median TTPD was 6.0 months in the chemonaïve group and 4.9 months in the pretreated group (Figure 2). Median survival could not be estimated in the pretreated group because of a high censoring rate (78.9%); however, the 1-year survival rate was 54.7%.

Per an intent-to-treat analysis, median survival was also estimated for all treated patients with MPM who received single-agent pemetrexed (n = 812). For all treated patients in the chemonaïve group (n = 319), the median survival was 14.1 month (95% CI, 10.4 months–16.4 months) and the 1-year survival rate was 53.9% (95% CI, 41.7–66.2%). For all pretreated patients with MPM who received single-agent pemetrexed (n = 493), the median survival was 9.5 months (95% CI, 8.6 months–not estimable) and the 1-year survival rate was 47.2% (95% CI, 36.3–58.1%).

Safety

Only myelotoxicity data were collected. The most often reported CTCAE grade 3 and 4 toxicities observed in each group are summarized in Table 4. Of 319 chemonaïve patients and 493 pretreated patients, respectively, CTCAE grade 3/4 toxicities observed in >10% of the patients were neutropenia (17.3 and 15.6%) and leukopenia (14.7 and 13.9%).

SAEs, which were monitored by the Lilly Safety System, reported in ≥1% of patients in the chemonaïve group were: nausea (3.4%), vomiting (3.1%), thrombocytopenia (3.1%), anemia (1.6%), neutropenia (1.3%), and diarrhea (1.3%). SAEs reported in ≥1% of patients in the pretreated group were: anemia (2.2%), pancytopenia (1.6%), nausea (1.6%), vomiting (1.6%), neutropenia (1.0%), and sepsis (1.0%). During the study, 11 deaths were considered possibly related to study-drug toxicity by the investigators. Four of these deaths occurred in the chemonaïve group (1 each caused by neutropenic sepsis, pancytopenia, acute respiratory

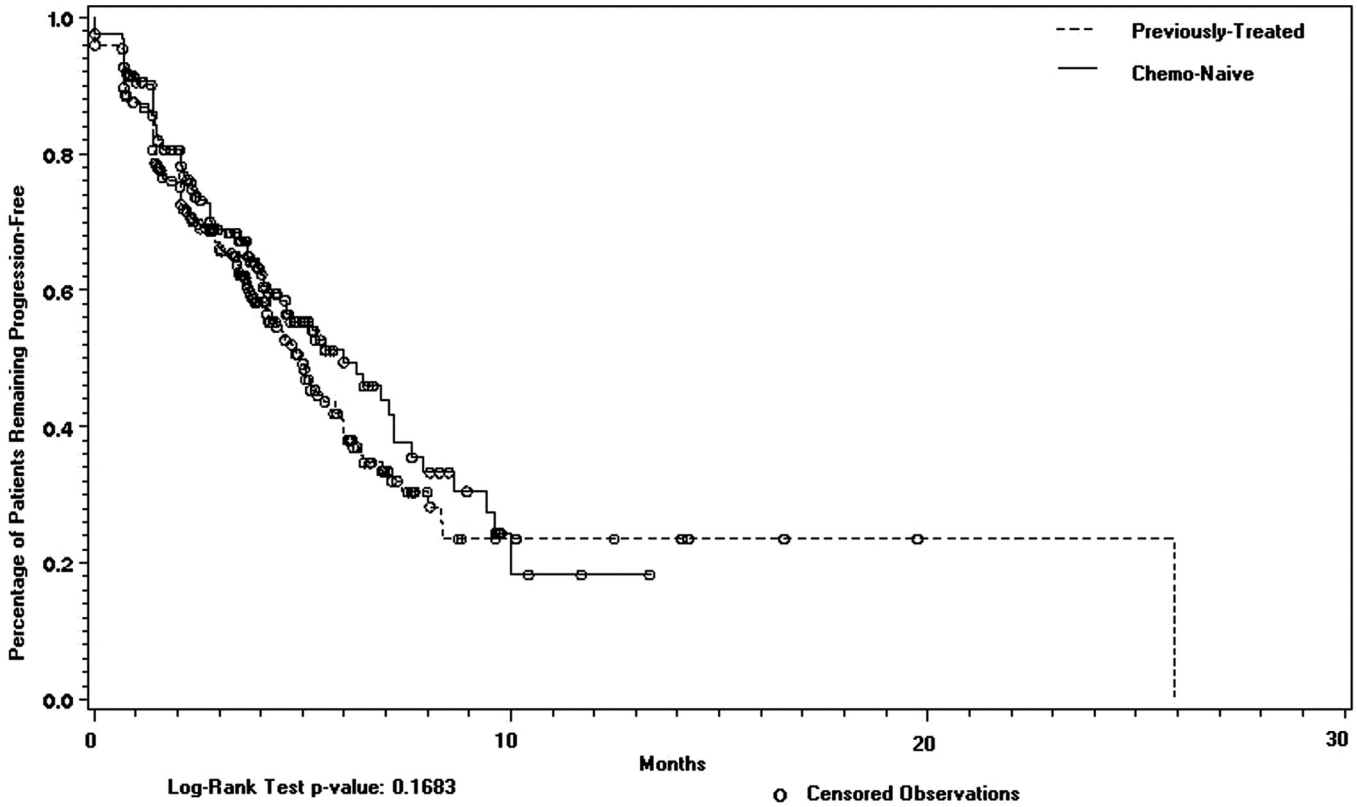

FIGURE 2. Kaplan-Meier analysis of time to progressive disease (months) in patients with MPM who received single-agent pemetrexed. Evaluable population consisted of chemonaïve patients (n = 247) and previously treated patients (n = 396).

TABLE 4. CTCAE Grade 3/4 Hematologic Toxicity in Patients who Received Single-agent Pemetrexed (Safety Population)

Toxicity[a]	Chemonaïve Patients (n = 319)[b]	Pretreated Patients (n = 493)[c]
Neutropenia, %	17.3	15.6
Leukopenia, %	14.7	13.9
Anemia, %	7.5	9.2
Thrombocytopenia, %	2.9	4.9

[a] Only myelosuppression data were collected.
[b] Of the 319 chemonaïve patients, 301 patients had at least one observation for neutrophils, and 306 patients had at least one observation for the other 3 toxicity parameters.
[c] Of the 493 pretreated patients, 461 patients had at least one observation for neutrophils, and 469 patients had at least one observation for the other 3 toxicity parameters.
CTCAE, Common Terminology Criteria for Adverse Events; *n,* number of patients.

failure, and unknown cause), and 7 deaths occurred in the pretreated group (2 caused by neutropenic sepsis, 2 caused by septic shock, and 1 each caused by ileus, sepsis, and pancytopenia).

DISCUSSION

The phase III randomized study reported by Vogelzang et al. demonstrated that the combination of pemetrexed and cisplatin was more effective than cisplatin monotherapy in MPM. Although the combination was associated with higher response rates and improved survival and quality of life,[17] platinum-containing regimens may be inappropriate for elderly patients with comorbidities and a poor performance status.

In the current European EAP, chemonaïve and pretreated patients with MPM who received single-agent pemetrexed demonstrated similar response rates of 10.5 and 12.1%, and a 1-year survival rate of 58.6 and 54.7%, respectively. In addition, the median survival time of 14.1 month in the chemonaïve group was notable.

Comparing response rates observed in the present EAP with those reported for other clinical studies presents a challenge since the protocol did not use the now widely accepted "modified RECIST" guidelines. The EAP protocol was less restrictive and allowed the use of RECIST, Southwest Oncology Group, or World Health Organization criteria to assess response. Still, the present EAP demonstrated higher response rates and longer survival as compared with a similar EAP conducted in the United States (Table 5), which allowed similar flexibility in the criteria used to evaluate response in MPM.[24,25] In the United States EAP, the response rate for chemonaïve and pretreated patients was 6.7%[24] and 5.5%,[25] and respective median survival times were 4.8 months[24] and 4.1 month.[25] The observed differences in efficacy between the two programs could be related to differences in population characteristics such as age, performance status, and regional or ethnic characteristics. A multicenter phase II study in 43 vitamin-supplemented chemonaïve patients receiving single-agent pemetrexed showed a response rate that was similar to the present study (Table 5).[13] Studies evaluating other antifolates (raltitrexed, trimetrexate, edatrexate, and methotrexate) in chemonaïve patients reported higher overall response rates, from 12 to 37%, than this European EAP. Overall survival times of 7 to 11 months were, however, shorter than in the present EAP (Table 5).[7–10] In a randomized phase III study of single-agent pemetrexed with best supportive care (BSC) versus BSC for second-line chemotherapy in patients with MPM,[26] the overall response rate (19.2 versus 1.7%) and median TTPD (3.8 months versus 1.5 months) were in favor of the pemetrexed with BSC arm. The median survival (8.6 versus 9.7 months), however, was not significantly different on the two arms, probably because of the use of poststudy chemotherapy in the BSC arm. Sorensen et al. studied the feasibility of single-agent pemetrexed as second-line therapy for patients with MPM who had previously received a platinum-based regimen.[27] For these 28 patients who received pemetrexed as second-line chemotherapy, the response rate, median survival, and 1-year survival rate was 21%, 9.8 months, and 36%, respectively. Another study demonstrated the role of single-agent pemetrexed as maintenance therapy in patients with MPM.[28] Although only 27

TABLE 5. Studies of Single-agent Antifolates in Chemonaïve Patients with Malignant Pleural Mesothelioma

Agent	Authors	No. of Pts	Overall Response Rate (%)	Median Survival (mo)	One-year Survival Rate (%)
Pemetrexed (current EU EAP)	Taylor et al.	812	10.5	14.1	53.9
Pemetrexed (US EAP)	Obasaju et al.[24]	19	6.7	4.8	0
Pemetrexed	Scagliotti et al.[13]	64	14.1	10.7	47.8
Raltitrexed	Baas et al.[7]	24	20.8	7.0	NA
Edatrexate	Kindler et al.[9]	20	25.0	9.6	50.0
Trimetrexate	Vogelzang et al.[8]				NA
Low-dose cohort		17	12.0	5.0	
High-dose cohort		35	12.0	8.9	
Methotrexate	Solheim et al.[10]	63	37.0	11.0	NA (2-yr = 32)

No., number; Pts, patients; EAP, expanded access program; NA, not available or not reported.

patients were enrolled in that study, the findings suggest that patients who received single-agent pemetrexed as maintenance therapy (range of 8–20 cycles) had approximately 3-fold longer time to progression and survival.

Hematologic toxicity observed in the EAP was mild, and similar to that seen in a previously reported phase II study of single-agent pemetrexed.[13] Likewise, the incidence of SAEs in this large group of patients was comparatively low, especially given that these patients were not considered suitable for pemetrexed plus platinum combination therapy. A substantial number of patients in the present EAP, in both the chemonaïve and the pretreated groups, received 6 or more cycles of chemotherapy, suggesting that single-agent pemetrexed was generally well tolerated. The tolerability of pemetrexed allows prolonged administration of this agent, which may translate to prolonged survival.

The efficacy and safety results of this EAP supplement the current clinical information regarding the use of pemetrexed in MPM. Although the overall response rate was low compared with previous reports, the median TTPD (6.0 months and 4.9 months) and 1-year survival rates (58.6 and 54.7%) were respectable in both chemonaïve and pretreated patients with MPM. Hematologic toxicity was mild. Important limitations of this study restrict how broadly these results can be generalized. One inherent weakness of a compassionate-use program is that certain data are not rigorously collected. An inordinately large percentage of patients had a histologic diagnosis of "other," for example, making it difficult to assess the baseline condition of these patients relative to patient groups described in previous studies. In addition, tumor response designations could have been applied inconsistently because the study protocol allowed for several different methodologies to evaluate response. Response rates for pretreated patients should be interpreted with greater caution since having a response to prior therapy could have affected the likelihood of response in this EAP. Although prior treatment with pemetrexed was allowed, the timing and logistics of this program suggest that a relatively small proportion of patients received this agent as prior therapy. Despite these limitations, the results presented here appear to confirm, in a community setting, the activity of single-agent pemetrexed and suggest a possible role for this regimen in patients with MPM who cannot tolerate platinum-based therapy.

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