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ORIGINAL REPORT

Phase III Trial of Pemetrexed Plus Best Supportive Care Compared With Best Supportive Care in Previously Treated Patients With Advanced Malignant Pleural Mesothelioma

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ABSTRACT

Purpose
This multicenter, phase III study compared overall survival (OS) of second-line pemetrexed plus best supportive care (BSC) versus BSC alone in patients with advanced malignant pleural mesothelioma (MPM). Secondary end points included response rate, progression-free survival (PFS), time to tumor progression (TTP), time to treatment failure (TTF), and toxicity.

Patients and Methods
Patients with relapsed MPM after first-line chemotherapy were randomly assigned to receive pemetrexed 500 mg/m^2 plus BSC (P+BSC) every 21 days or BSC alone.

Results
The study enrolled 243 patients (123 on P+BSC arm and 120 on BSC arm). Median OS time was not significantly different between the arms (8.4 months for P+BSC and 9.7 months for BSC; $P = .74$). Cox regression modeling suggested a trending survival benefit for patients who responded to first-line therapy. Time-to-event measures significantly favored P+BSC (median PFS, TTP, and TTF). Partial response was achieved in 18.7% and 1.7% of patients in P+BSC and BSC arms, respectively ($P < .0001$), and a disease control rate (partial response plus stable disease) was achieved in 59.3% and 19.2% of patients in P+BSC and BSC arms, respectively ($P < .0001$). Use of postdiscontinuation chemotherapy was significantly greater among BSC patients compared with P+BSC patients (51.7% *v* 28.5%, respectively; $P = .0002$), with more BSC patients receiving pemetrexed (18.3% *v* 3.3%, respectively; $P = .0001$). Postdiscontinuation therapy was initiated earlier for BSC than P+BSC patients (median time to initiation, 4.3 *v* 15.7 months, respectively; log-rank $P < .0001$). Chemotherapy was well tolerated, with expected modest (4% to 7%) grade 3 and 4 hematologic toxicities.

Conclusion
Second-line pemetrexed elicited significant tumor response and delayed disease progression compared with BSC alone in patients with advanced MPM. Improvement in OS was not seen in this study, possibly because of the significant imbalance in postdiscontinuation chemotherapy between the arms.

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INTRODUCTION

Malignant pleural mesothelioma (MPM) is a locally invasive, usually fatal neoplasm arising from the mesothelial surfaces of the pleural cavity. Until recently, treatment of MPM has not routinely included chemotherapy, even though few patients qualify for curative surgery and the efficacy of radiotherapy is limited. After two decades of testing, the chemotherapeutic agents doxorubicin, cisplatin, carboplatin, and ifosfamide have each shown modest activity. More recently, gemcitabine and antimetabolites (eg, raltitrexed) have also shown modest activity in phase II studies (< 20% response rate). Combination doublets containing an antimetabolite and a platinum have shown the greatest promise.[1-5] The combination of the antifolate pemetrexed and cisplatin demonstrated improved survival, time to progression, response rate, pulmonary function, and symptom control compared with cisplatin alone[4] and is currently approved as first-line chemotherapy in 82 countries worldwide. In a recent phase II study, pemetrexed plus carboplatin yielded similar efficacy results.[6]

Most MPM chemotherapy trials have focused on chemotherapy-naive patients; however, patients

benefiting from first-line treatment are still relatively fit when progression occurs and thus are potential candidates for second-line chemotherapy. In a retrospective study, Manegold et al[7] examined the cohort of 189 patients receiving poststudy chemotherapy after the pemetrexed/cisplatin registration trial. Poststudy chemotherapy was associated with statistically significant prolonged survival, although causality could not be concluded. A few small MPM studies have examined the safety and efficacy of second-line therapy with mixed results.[8-13]

This multicenter, phase III study was designed to compare the efficacy and safety of second-line chemotherapy with pemetrexed and best supportive care (P+BSC) versus best supportive care (BSC) alone in advanced MPM. Pemetrexed was chosen because of its efficacy as a single agent in the first-line setting[14] and because, at the time of trial initiation, many MPM patients were not receiving pemetrexed as first-line treatment. The primary end point was overall survival (OS); secondary end points were response rate, other time-to-event variables, quality-of-life assessment, and toxicity.

PATIENTS AND METHODS

Eligibility Criteria

Patients ≥ 18 years old with histologically diagnosed advanced MPM and one prior systemic chemotherapy regimen (excluding pemetrexed) for advanced or metastatic disease were enrolled. Patients were required to have unidimensionally and/or bidimensionally measurable disease; a Karnofsky performance score ≥ 70; adequate bone marrow reserve (absolute neutrophil count ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L, and hemoglobin ≥ 9 g/dL); creatinine clearance ≥ 45 mL/min, calculated by the modified Cockcroft and Gault lean body mass formula[15]; and estimated life expectancy ≥ 8 weeks. Prior radiation to less than 25% of the bone marrow and pleurodesis were allowed if completed ≥ 14 days before study.

Written informed consent was obtained from all patients before enrollment. The study was conducted following the guidelines of good clinical practice or the Helsinki Declaration (whichever offered greater protection to the patient), was approved by each institution's ethics committee, and was monitored by the institutional review board where appropriate.

Study Design and Treatment Plan

This was a phase III, multicenter, open-label, randomized study of P+BSC versus BSC with a target enrollment of 240 patients. Patients were randomly assigned to P+BSC or BSC via a centralized randomization system. A minimizing algorithm[16] (probability factor, 0.75) was applied to balance the treatment arms for histologic subtype (epithelial or all other types), prior raltitrexed therapy, Karnofsky performance score (70 to 80 *v* 90 to 100), sex, WBC count (≥ 8.3×10^9/L *v* < 8.3×10^9/L), and institution.

Patients on the BSC arm received treatment administered with the intent to maximize quality of life without a specific antineoplastic regimen. This included antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis. BSC excluded surgery, immunotherapy, anticancer hormonal therapy, systemic chemotherapy, and radiotherapy (except palliative). Patients on the BSC arm were assessed at 3-week intervals and remained on study for 24 weeks (corresponding to eight cycles) unless progressive disease (PD) or early discontinuation occurred. Postdiscontinuation assessments occurred every 6 weeks until PD and then every 90 days until death. There were no restrictions on either arm as to type or timing of poststudy treatment. Response to poststudy chemotherapy was not collected.

Pemetrexed (Alimta; Eli Lilly & Co, Indianapolis, IN) 500 mg/m^2 was administered to patients on the P+BSC arm as a 10-minute intravenous infusion on day 1 of a 3-week cycle. Treatment continued for eight cycles unless PD occurred or the investigator or patient decided to discontinue treatment. Additional cycles were allowed if the patient had shown clinical benefit. Postdiscontinuation assessments occurred at the same intervals as for BSC patients. P+BSC patients were administered oral folic acid (350 to 1,000 μg daily), beginning 1 to 2 weeks before the first pemetrexed dose until 3 weeks after the final dose. Vitamin B_{12} (1,000 μg intramuscular injection) was administered 1 to 2 weeks before the first pemetrexed dose and every 9 weeks thereafter until 3 weeks after the final dose. Dexamethasone (4 mg or equivalent) was administered orally twice daily, beginning the day before and ending the day after each pemetrexed dose.

Pemetrexed doses were delayed if neutrophils or platelets decreased to less than baseline levels. Dose modifications occurred for neutrophil levels of less than 0.5×10^9/L and platelet levels of 50 to 100×10^9/L (25% reduction) or platelet levels of less than 50×10^9/L (50% reduction). Treatment was delayed for grade 3 or 4 nonhematologic toxicities (except grade 3 transaminase elevation, nausea, or vomiting) or calculated creatinine clearance of less than 45 mL/min. When nonhematologic toxicities resolved, doses were resumed at 25% reduction. Dose re-escalation was not allowed. Any patient requiring a third dose reduction or treatment interruption ≥ 42 days had treatment discontinued. Patients on the P+BSC arm could receive granulocyte colony-stimulating factors for neutrophil levels less than 0.5×10^9/L, neutropenic fever, or neutropenic infection. Leucovorin could be administered for grade 4 leukopenia or neutropenia lasting ≥ 3 days, grade 4 thrombocytopenia, grade 3 thrombocytopenia with associated bleeding, or grade 3 or 4 mucositis.

Study Evaluation

Baseline tumor measurements were taken ≤ 4 weeks before enrollment via computed tomography or magnetic resonance imaging. Change in disease was assessed by measuring the thickness of up to three involved areas of pleural rind at each of three separate levels, with levels at least 2 cm apart and with at least one lesion more than 1.5 cm. The same baseline tumor assessment method was repeated every 6 weeks for both arms. Tumor response was confirmed 3 to 4 weeks after first evidence and every 6 weeks thereafter using Southwest Oncology Group criteria modified to allow unidimensional measurable disease.[17]

The primary efficacy end point was OS, which was defined as time from random assignment to death. The secondary end points and the intervals they measured were as follows: time to tumor progression (TTP), interval from random assignment to first observation of PD; progression-free survival (PFS), interval from random assignment to the first observation of PD or death; duration of response, interval from first observation of response to first observation of PD or death; and time to treatment failure (TTF), interval from random assignment to the first observation of PD, death, or early discontinuation. All time-to-event end points were censored at last visit date for patients who did not experience that event.

Quality-of-life assessment used the Lung Cancer Symptom Scale (LCSS), which consists of nine 100-mm visual analog scales, with scores reported from 0 to 100 (0 representing the best score).[18] Patient data were analyzed if a baseline assessment and at least one postbaseline assessment were available. The average symptom burden index (ASBI) was defined as the mean of six symptom-specific LCSS questions. If less than six questions were completed, the ASBI was not calculated, and four consecutive ASBI scores were required to calculate a change in ASBI. LCSS assessments were completed before each cycle (P+BSC arm) or 3-week assessment (BSC arm).

Body-surface area calculations, body weight, and clinical laboratory tests (hematology and blood chemistry) were completed at baseline and before each cycle or assessment. P+BSC patients also had creatinine clearance calculated using the Cockcroft-Gault algorithm[15] before each cycle and hematology at days 8 and 15 and blood chemistries at day 8 of each cycle. For both arms, BSC resource utilization and toxicities (National Cancer Institute Common Toxicity Criteria, version 2.0) were noted before each cycle or assessment.

Statistical Considerations

The planned sample size was 240 patients (120 patients per arm), which was chosen to provide 80% power to detect a 2-month improvement in median OS for P+BSC compared with BSC using the two-sided log-rank test (significance level, $P = .05$). All randomly assigned patients (intent-to-treat

population) were assessable for efficacy analysis; all BSC patients and those P+BSC patients who received at least one pemetrexed dose were assessable for safety. Survival and the distribution of time-to-event end points were estimated using the Kaplan-Meier method[19] and compared using the log-rank test.[20] Response rates and other proportions were compared using the χ^2 test.[21] Calculation of *P* values, point estimates, CIs, and least squares means were performed using SAS version 8 (SAS Institute, Cary, NC).

RESULTS

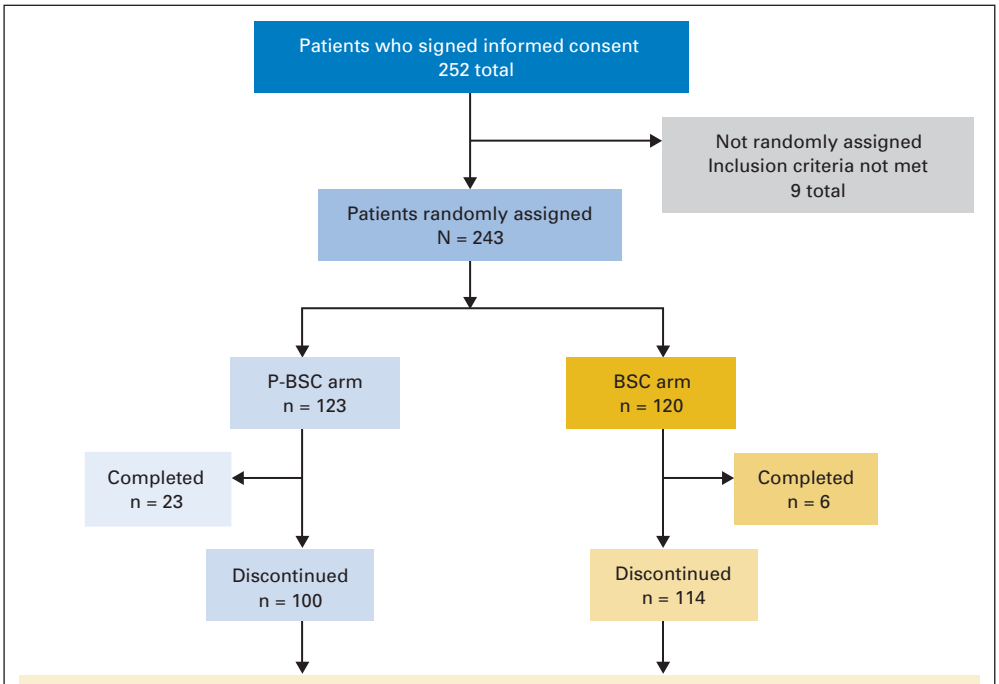
Patient Characteristics

Between October 2001 and June 2004, 45 institutions worldwide entered 252 patients onto this study. Nine patients did not meet inclusion criteria and were not randomly assigned. The remaining 243 patients were randomly assigned to the P+BSC arm (123 patients) and the BSC arm (120 patients; Fig 1). The two treatment arms were similar in patient composition, including best response to prior chemotherapy (Table 1) and types of prior chemotherapy (data not shown). Both arms had a similar mean interval from date of progression after prior chemotherapy to date of random assignment to this study (P+BSC arm: 2.1 months; BSC arm: 2.0 months).

Treatment

Of the 123 P+BSC patients, 121 received at least one dose of pemetrexed. Two patients did not receive pemetrexed, one because of protocol violation and the other because of death from PD before cycle 1. In total, P+BSC patients received 606 pemetrexed doses. A median of five cycles per patient was administered (range, one to 34 cycles), corresponding to 99.2% of the planned dose, with no dose omissions. Eight (6.6%) of the 121 P+BSC patients accounted for the 10 dose reductions (neutropenia, n = 3; fatigue, n = 2; febrile neutropenia, n = 2; and leukopenia, gamma-glutamyltransferase increase, or AST increase, n = 1 each). Nineteen doses were delayed for clinical reasons, including fatigue (n = 3), decreased creatinine clearance (n = 2), and edema (n = 2).

Twenty-three P+BSC patients completed eight or more cycles, and six BSC patients remained on study for eight or more cycle equivalents (24 weeks). Efficacy assessments were performed on both arms at similar median intervals (1.7 months for P+BSC, 1.6 months for BSC). Most patients on both arms discontinued treatment early as a result of PD (P+BSC: 72 patients, 58.5%; BSC: 67 patients, 55.8%) or death from MPM (P+BSC: 12 patients, 9.8%; BSC: 14 patients, 11.7%). Additionally, four P+BSC patients



Reason for discontinuation, n(%)	P-BSC	BSC
Adverse event	3 (2.4)	0
Satisfactory response, patient and/or physician perception	3 (2.4)	0
Lack of efficacy, patient and/or physician perception	3 (2.4)	2 (1.6)
Personal conflict or other patient decision	4 (3.3)	22 (18.3)
Unable to contact patient (lost to follow-up)	0	3 (2.5)
Lack of efficacy, progressive disease	72 (58.5)	67 (55.8)
Lack of efficacy, stable disease	0	1 (0.8)
Death from study disease	12 (9.8)	14 (11.7)
Patient received other anti-cancer intervention, not allowed	0	2 (1.6)
Other (protocol violation, death due to other cause, protocol entry criteria not met)	3 (2.4)	3 (2.4)

Fig 1. CONSORT diagram. P, pemetrexed; BSC, best supportive care.

Table 1. Patient Demographics and Baseline Characteristics

Variable	P+BSC (n = 123) No. of Patients	%	BSC (n = 120) No. of Patients	%
Age, years				
Median	60		61	
Range	32-78		33-79	
Race				
White	110	89.4	108	90.0
Hispanic	8	6.5	9	7.5
Other	5	4.1	3	2.5
Sex				
Male	96	78.0	93	77.5
Female	27	22.0	27	22.5
Disease stage				
IA, IB, II	13	10.6	14	11.7
III	34	27.6	36	30.0
IV	76	61.8	70	58.3
Histology				
Epithelial	90	73.2	86	71.7
Other	33	26.8	34	28.3
Karnofsky performance score*				
90-100	60	48.8	60	50.0
50-80	61	49.6	52	43.3
Unknown	2	1.6	8	6.7
Response to prior chemotherapy				
CR	2		3	
PR	23		25	
SD	50		50	
PD	39		36	
Not assessable, not determined, unknown	9		6	

Abbreviations: P, pemetrexed; BSC, best supportive care; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*One additional patient on each treatment arm had a performance status of either 50 or 60.

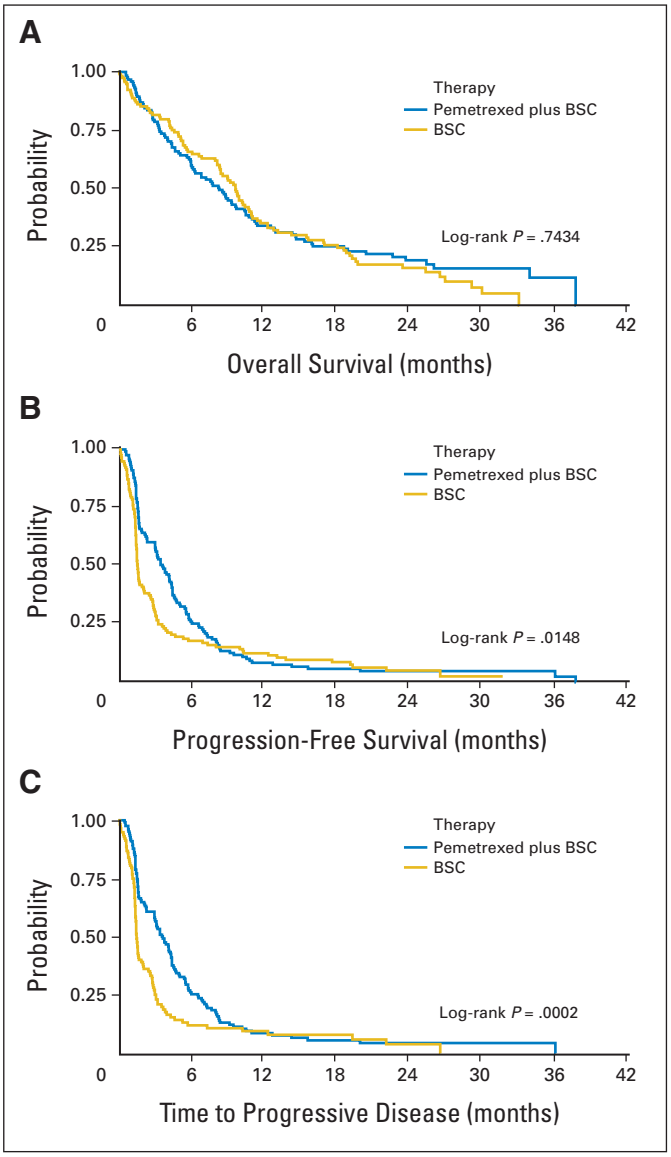


Fig 2. (A) Overall survival. (B) Progression-free survival. (C) Time to progressive disease. BSC, best supportive care.

(3.3%) and 22 BSC patients (18.3%) discontinued treatment early as a result of other nonsafety-related reasons (Fig 1).

Efficacy

The survival analysis was performed with a 23% censoring rate on both arms. The median follow-up time for survival was 14.5 months. Median OS time was 8.4 months (95% CI, 6.2 to 10.5 months) for P+BSC patients and 9.7 months (95% CI, 8.4 to 10.9 months) for BSC patients ($P = .7434$; Table 2 and Fig 2A), with a hazard ratio of 0.95 (95% CI, 0.71 to 1.27). The time-to-event variables of PFS, TTP, and TTF significantly favored the P+BSC arm (Table 2, Figs 2B and 2C).

Response rate also significantly favored the P+BSC arm. Twenty-three P+BSC patients (18.7%) were responders (all partial

Table 2. Time-Related Efficacy Results

Variable	P+BSC (n = 123) Median	95% CI	BSC (n = 120) Median	95% CI	Log-Rank *P*
Median survival, months	8.4	6.2 to 10.5	9.7	8.4 to 10.9	.7434
Median progression-free survival, months	3.6	3.0 to 4.4	1.5	1.5 to 1.9	.0148
Median time to tumor progression, months	3.7	3.0 to 4.4	1.5	1.4 to 1.7	.0002
Median time to treatment failure, months	3.6	3.0 to 4.4	1.5	1.4 to 1.6	< .0001

Abbreviations: P, pemetrexed; BSC, best supportive care.

responses [PRs]) compared with two BSC patients (1.7%; $P < .0001$; Table 3). The median duration of response for P+BSC patients was 5.5 months (95% CI, 4.2 to 7.8) months. When OS was assessed for the P+BSC responders, the median OS time increased from 8.4 to 20.5 months (95% CI, 12.9 to 25.5 months; Table 3). Furthermore, 50 P+BSC patients (40.7%) reported stable disease (SD) compared with 21 BSC patients (17.5%), yielding a disease control rate (PR+SD) of 59.3% and 19.2%, respectively ($P < .0001$). The BSC arm had a disproportionate number of patients who discontinued from the study before response determination (response listed as unknown).

To examine the survival data further, Cox regression modeling was used to examine treatment by factor interaction for OS for a set of baseline factors. The analysis revealed that only best response to prior chemotherapy (complete response, PR, or SD *v* PD or unknown/not assessable) had a significant interaction effect ($P = .03$). Further subgroup analysis showed that pemetrexed may have a trending survival benefit for patients who had a best response of SD or better to prior chemotherapy (hazard ratio, = 0.734; 95% CI, 0.51 to 1.05; $P = .09$).

Postdiscontinuation Chemotherapy

As detailed in Table 4, significantly more BSC patients (51.7%) than P+BSC patients (28.5%) received postdiscontinuation chemotherapy ($P = .0002$). The percentage of BSC patients who received pemetrexed after discontinuing from study treatment was also much higher (18.3% *v* 3.3%, respectively; $P = .0001$). Furthermore, BSC patients received postdiscontinuation chemotherapy significantly earlier than P+BSC patients (median time to initiation, 4.3 *v* 15.7 months, respectively; log-rank $P < .0001$).

Quality of Life

There was no statistically significant difference between the arms in mean change from baseline among any of the LCSS questions. As a result of higher patient dropout on the BSC arm, an insufficient number of patients had four consecutive ASBI scores required to assess this quality-of-life parameter.

Safety

For P+BSC patients, grade 3 or 4 toxicities were primarily hematologic, whereas no grade 3 or 4 hematologic toxicities occurred among BSC patients (Table 5). The seven P+BSC patients with grade 3 or 4 anemia were among the 13 P+BSC patients (10.7%) who received one or more transfusions while on study. One patient received RBCs and platelets, and 12 patients received RBCs only.

Other grade 3 or 4 toxicities on the P+BSC arm included febrile neutropenia (four patients, 3.3%) and an approximate 5% increase in fatigue and chest pain compared with BSC patients. No treatment-related deaths occurred on either arm. Three P+BSC patients discontinued treatment, including two patients as a result of treatment-related adverse events (grade 1 and grade 2 decrease in creatinine clearance).

Table 4. Postdiscontinuation Chemotherapy

Chemotherapy Type	P+BSC (n = 123) No. of Patients	P+BSC (n = 123) %	BSC (n = 120) No. of Patients	BSC (n = 120) %
Patients receiving at least one chemotherapy agent*	35	28.5	62	51.7
Chemotherapy†				
Platinums	14	11.4	23	19.2
Anthracyclines	16	13.0	12	10.0
Pemetrexed	4	3.3	22	18.3
Gemcitabine	7	5.7	15	12.5
Vinorelbine	6	4.9	9	7.5
Other agents	2	1.6	6	5.0
Raltitrexed	3	2.4	3	2.5
Mitomycin	0	0	3	2.5
Docetaxel	1	0.8	1	0.8

Abbreviations: P, pemetrexed; BSC, best supportive care.
*$P = .0002$.
†Patients may have received more than one of these therapies.

DISCUSSION

Given the natural rapid progression of MPM, with most patients dying within 1 year of diagnosis,[22] the role of a second-line chemotherapy

Table 3. Response Rates

Best Study Response	P+BSC (n = 123) No. of Patients	P+BSC (n = 123) %	BSC (n = 120) No. of Patients	BSC (n = 120) %
CR	0		0	
PR	23	18.7	2	1.7
SD	50	40.7	21	17.5
PR+SD	73	59.3	23	19.2
PD	43	35.0	69	57.5
Unknown*	7	5.7	28	23.3
Duration of response (CR+PR), months				
Median	5.5		NA†	
95% CI	4.2 to 7.8			
Overall survival for responders (CR+PR), months				
Median	20.5		NA†	
95% CI	12.9 to 25.5			

Abbreviations: P, pemetrexed; BSC, best supportive care; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not assessable.
*The majority of the patients with a best study response of unknown discontinued the study after 1 cycle (personal conflict/other patient decision) and before response could be assessed.
†There were too few patients with PR to calculate median time.

Table 5. Grade 3 or 4 Toxicity* Data With > 2% Incidence in Either Arm

Toxicity	P+BSC (n = 121)		BSC (n = 120)	
	No. of Patients†	%	No. of Patients†	%
Hematologic				
Neutropenia	9	7.4	0	0
Anemia	7	5.8	0	0
Leukopenia	5	4.1	0	0
Thrombocytopenia	5	4.1	0	0
Nonhematologic				
Dyspnea	21	17.4	19	15.8
Fatigue	19	15.7	13	10.8
Chest pain	17	14.0	10	8.3
Tumor pain	8	6.6	5	4.2
Hypertension	7	5.8	12	10.0
Pleuritic pain	5	4.1	5	4.2
Anorexia	5	4.1	3	2.5
Febrile neutropenia	4	3.3	0	0
Constitutional symptoms, other	4	3.3	3	2.5
Thrombosis/embolism	3	2.5	4	3.3
Cough	3	2.5	2	1.7
Nausea	3	2.5	0	0
Vomiting	3	2.5	0	0
Supraventricular arrhythmias	3	2.5	0	0
Pulmonary, other	1	0.8	3	2.5
Infection without neutropenia	0	0	3	2.5

Abbreviations: P, pemetrexed; BSC, best supportive care.
*According to National Cancer Institute Common Toxicity Criteria, version 2.0.
†Patients may have exhibited more than one type of toxicity.

has been questioned. This phase III study demonstrated that second-line chemotherapy can delay disease progression for advanced MPM patients. Patients on the P+BSC arm showed longer TTP, TTF, and PFS compared with patients treated with BSC alone. Furthermore, almost one fifth of the patients receiving P+BSC responded, and an additional 41% exhibited SD; thus, approximately 60% of the patients experienced temporary disease control compared with approximately 20% of patients on the BSC arm. Although pemetrexed administration delayed disease progression, it did not lengthen survival in this study. Responders on the P+BSC arm did exhibit markedly increased survival (to 20.5 months), although this is not necessarily exclusively a treatment effect. No difference between treatment arms was found for quality-of-life measurements; however, this assessment was hindered in part by a higher patient dropout rate on the BSC arm. Other studies have found that MPM patients who demonstrate improved survival and/or a tumor response after chemotherapy also show improvement in some quality-of-life parameters.[3,23-25] Chemotherapy was well tolerated, with expected modest (4% to 7%) grade 3 and 4 hematologic toxicities.

A recent study of the US pemetrexed expanded access program reported treatment outcomes of 91 MPM patients who received pemetrexed as second-line chemotherapy.[26] OS for the treated cohort was 4.1 months (95% CI, 3.2 months to not assessable). Of the 73 patients assessable for response, 5.5% exhibited a PR, and 41.1% had SD. Not surprisingly, these results are lower than those reported here. Entry criteria for an expanded access program are always less stringent than those of a prospectively planned clinical trial; hence, a direct comparison between the studies is difficult.

The determination that survival was not significantly different between the two arms in this study ($P = .7434$) was based on the unadjusted log-rank test, which does not adjust for any imbalance of potential influencing factors. However, various postdiscontinuation chemotherapy attributes were significantly imbalanced, including the proportion of patients receiving chemotherapy after discontinuing from the study, the median time to initiating poststudy chemotherapy, and the percentage of patients receiving pemetrexed as postdiscontinuation therapy. (The latter imbalance was a result of pemetrexed becoming commercially available during trial accrual.) These imbalances might have obscured a survival benefit.

Cox regression modeling demonstrated a potential benefit of pemetrexed in patients with at least SD in response to first-line treatment. This result is in keeping with the general observation that patients who are primarily chemotherapy resistant respond less frequently to second-line chemotherapy and may suggest potential utility for P+BSC among the subset of patients who responded to first-line chemotherapy.

In conclusion, MPM patients receiving second-line therapy with P+BSC exhibited significant antitumor activity (response rate, 18.7%), improved disease control rate (59.3% for P+BSC *v* 19.2% for BSC), and longer PFS, TTP, and TTF than patients receiving BSC alone. Although survival was not improved, the use of postdiscontinuation chemotherapy might have obscured this result. Additionally, second-line pemetrexed is more likely to yield a clinical benefit among patients who responded to first-line chemotherapy. The therapy was well tolerated, with qualitative and quantitative toxicities consistent with the known toxicity profile of pemetrexed. Further drug development is needed for these patients, with new treatments tested in well-controlled trials that account for the contribution of poststudy therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).