Pemetrexed as Second-Line Treatment in Malignant Pleural Mesothelioma after Platinum-Based First-Line Treatment

Jens Benn Sørensen, MD, DMSc, MPA, Stein Sundstrøm, MD, DMSc,† Katharina Perell, MD,* and Anne-Kathrine Thielsen, MD**

Introduction: Pemetrexed is active as first-line treatment of malignant pleural mesothelioma. The objective was to evaluate its activity as second-line treatment.

Methods: Patients had disease progression of malignant pleural mesothelioma after previous platinum-based regimens without pemetrexed. Treatment was pemetrexed alone or pemetrexed combined with carboplatin. Pemetrexed dosing was 500 mg/m^2 and carboplatin was AUC (area under the curve) 5 once every 3 weeks.

Results: Thirty-nine patients were included: 28 Danish patients received pemetrexed (three patients received pemetrexed as third-line treatment), whereas 11 Norwegian patients received pemetrexed plus carboplatin. Most patients were men (90%), had epithelial subtype (85%), and International Mesothelioma Interest Group stages III to IV (77%). Median age was 62 years (range, 30–77). The median number of treatment courses was six (range, 1–23). Common Toxicity Criteria grade 3 to 4 toxicity occurred only with respect to leukocytopenia (pemetrexed: 14% of patients; pemetrexed plus carboplatin: 9%) and thrombocytopenia (pemetrexed: 7%; pemetrexed plus carboplatin: 18%). One patient receiving pemetrexed died of sepsis. Partial response rates were 21% and 18%, the median time to progression was 21 weeks (range, 4–92) and 32 weeks (range, 4–128+), and the median survival was 42 weeks (range, 4–99) and 39 weeks (range, 10–128+) with pemetrexed and pemetrexed plus carboplatin, respectively.

Conclusions: Pemetrexed was generally well tolerated with noteworthy activity in malignant pleural mesothelioma after previous platinum-based treatment and may be considered for second-line treatment.

Key Words: Alimta, Pemetrexed, Pleural mesothelioma, Second-line treatment.

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*Department of Oncology, Finsen Centre/National University Hospital, Copenhagen, Denmark; †Department of Oncology, St. Olav Hospital, Trondheim, Norway.

Address for correspondence: Jens Benn Sørensen, MD, Department of Oncology, Finsen Centre/National University Hospital, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark. E-mail: jbsonk@rh.dk

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Malignant pleural mesothelioma (MPM) is a lethal lesion in most cases, and only a few patients are eligible for curative surgery.[1] The median survival is 12 months, but only 12% of patients with poor prognostic factors survive 1 year.[2] Chemotherapy for MPM is challenging, although several cytotoxic agents have been tested and the rates of objective tumor response have ranged from 10% to 30% with monotherapy.[3] Cisplatin and carboplatin are both active and thus included in the most used combination regimens for MPM.[4] Pemetrexed is a multitargeted antifolate with a 14% response rate as a single agent in chemotherapy-naive MPM patients.[5] Recently, a large randomized trial demonstrated that combination chemotherapy with pemetrexed and cisplatin significantly increased both survival time (from 9.3 to 12.1 months) and time to progression (from 3.9 to 5.7 months) compared with cisplatin monotherapy.[6] Thus, the combination of pemetrexed and cisplatin is a reference combination for first-line treatment of MPM.

Patients with progression after first-line treatment may often be in good health and commonly inquire about second-line treatment. Only few data are available to guide the oncologist in selecting such treatment because the vast majority of previously reported trials in MPM included solely previously untreated patients. Thus, it was the aim of this study to evaluate pemetrexed as second-line chemotherapy or beyond in MPM patients not previously exposed to this agent.

MATERIALS AND METHODS

Patients

Eligibility criteria included histologically proven MPM, progression after platinum-based combination chemotherapy, measurable disease, Eastern Cooperative Oncology Group performance status of 0 to 2, estimated survival expectancy of ≥3 months, age 18 years or older, and written informed consent.

Adequate organ functions were required, defined as white blood cell count ≥3000/μl, platelet count ≥100,000/μl, hemoglobin ≥9.0 g/dl, bilirubin <1.25 times the upper limit of normal, aspartate aminotransferase and alanine aminotransferase <2.5 times the upper limit of normal, and creatinine <2.0 mg/dl.

Exclusion criteria included previous exposure to pemetrexed, significant medical or psychiatric comorbidity, central nervous metastases, pregnant or lactating women, and history of cancers in the previous 5 years or breast cancer ever.

All women of reproductive age were to use safe contraception. The standards of Helsinki Declaration were fulfilled.

Treatment

Danish patients received pemetrexed monochemotherapy 500 mg/m^2 as a 10-minute infusion every 3 weeks. Norwegian patients received same dose of pemetrexed with carboplatin area under the curve (AUC) 5 (pemetrexed plus carboplatin), both administered day 1 every 3 weeks. The difference in treatment between Danish and Norwegian patients was solely a difference in general treatment strategy due to which Norwegian patients were reinduced with carboplatin after previous exposure to this agent, whereas this was not the strategy in Denmark. The two data sets were not part of a common study but were combined after treatment of the two cohorts.

Folic acid 400 μg/day orally and vitamin B_{12} 1000 mg administered intramuscularly every 9 weeks were used in both regimens, beginning 1 to 3 weeks before study start. Prednisolone 50 mg was administered twice daily on the day before, on the day of, and on the day after pemetrexed to reduce the risk of severe skin rash. Standard antiemetic prophylaxis with 5-hydroxytryptamine-3 antagonists and metoclopramide was administered before chemotherapy.

Before start of any cycle, the total leukocyte count had to be $\geq$3.0 x 10^9/liter, absolute neutrophil count $\geq$1.5 $\times$ 10^9/liter, and platelet count $\geq$100 $\times$ 10^9/liter. On recovery, patients with a nadir total leukocyte count $<$1.0 $\times$ 10^9/liter, absolute neutrophil count $<$0.5 $\times$ 10^9/liter, or platelet count $<$25 $\times$ 10^9/liter received 75% of the previous pemetrexed dose. In the event of grade 3 or 4 nonhematologic toxicities, treatment was delayed until there was resolution to grade 1 or less before proceeding. Therapy was then resumed at 75% of the previous dose level, if deemed appropriate by the treating physician. Dose delays up to 42 days were permitted for recovery from study drug toxicity. Dose escalations were not allowed.

TABLE 1. Characteristics for 39 Malignant Pleural Mesothelioma Patients Previously Treated with Platinum-Based Chemotherapy and Receiving Second- or Third-Line Treatment with Pemetrexed

	No. of Patients (%)		
	Pemetrexed (*n* = 28)	**Pemetrexed + Carboplatin (*n* = 11)**	**Total (n = 39)**
Gender, no. (%)			
Male	26 (93)	9 (82)	35 (90)
Female	2 (7)	2 (18)	4 (10)
Stage, no. (%)			
Ib	1 (4)	0	1 (3)
II	4 (14)	4 (36)	8 (20)
III	12 (43)	6 (55)	18 (46)
IV	11 (39)	1 (9)	12 (31)
Performance status, no. (%)			
0	8 (29)	1 (9)	9 (28
1	17 (61)	9 (82)	26 (67)
2	3 (11)	1 (9)	4 (10)
Histology, no. (%)			
Epithelial	22 (79)	11 (100)	33 (85)
Sarcomatous	1 (4)	0	1 (2)
Biphasic	5 (18)	0	5 (13)
Age, yr			
Median (range)	62 (30–73)	62 (43–77)	62 (30–77)
Lead time from diagnosis to study start (d)			
Median (range)	283 (86–956)	389 (174–778)	308 (86–956)
1st line treatment, no. (%)			
Vinorelbine + cisplatin	21 (75)	0	21 (54)
Vinorelbine + carboplatin	2 (7)	0	2 (5)
Gemcitabine + carboplatin	5 (18)	0	5 (13)
Gemcitabine + Caelyx + carboplatin	0	11 (100)	11 (28)
Response to 1st line, no. (%)			
0 (no)	22 (79)	7 (64)	28 (72)
1 (yes)	6 (21)	4 (36)	10 (21)
Pemetrexed treatment, no. (%)			
2nd line	25 (89)	11	36 (92)
3rd line	3 (11)	0	3 (8)

Caelyx, liposomal doxorubicin.

Assessments During Treatment

Baseline and predosing assessment included complete history and physical examination, complete blood cell count, calculated creatinine clearance, liver enzymes, blood electrolytes, blood albumin, calcium, and glucose. Survival was defined as the time from pemetrexed treatment start to the time of death from any cause. Time to disease progression was defined as the time from treatment start until documented progression or death from any cause. For patients without disease progression 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. Computed tomography was performed before every other treatment and every 2 months after completion of study therapy.

The new modified RECIST (Response Evaluation Criteria in Solid Tumors) criteria for the assessment of response in MPM were applied.[7] Change in disease was assessed by measuring the tumor thickness perpendicular to the chest wall or mediastinum in up to three involved areas of pleural rind at least 2 cm apart on computed tomography scan, at baseline,

TABLE 2. Toxicity (Common Toxicity Criteria Grading) with Pemetrexed in 39 Malignant Pleural Mesothelioma Patients Previously Treated with Platinum-Based Chemotherapy

	No. (%) of Patients		
	Pemetrexed (n = 28)	**Pemetrexed + Carboplatin (n = 11)**	**Total (n = 39)**
Nausea			
NA	0	3 (27)	3 (8)
0	16 (57)	6 (55)	22 (56)
1	9 (32)	0	9 (23)
2	2 (7)	2 (18)	4 (10)
3	1 (4)	0	1 (3)
Leukocytes			
NA	0	3 (27)	3 (8)
0	12 (43)	0	12 (31)
1	7 (25)	0	7 (18)
2	5 (18)	7 (64)	12 (31)
3	2 (7)	1 (9)	3 (8)
4	2 (7)	0	2 (5)
Thrombocytes			
NA	0	3 (27)	3 (8)
0	20 (71)	0	20 (51)
1	6 (21)	2 (18)	8 (21)
2	0	4 (36)	4 (10)
3	1 (4)	2 (18)	3 (8)
4	1 (4)	0	1 (3)
Febrile leukopenia			
NA	0	3 (27)	3 (8)
0 no	27 (96)	8 (73)	35 (92)
1 yes	1 (4)	0	1 (3)
Bleeding episodes			
NA	0	3 (27)	3 (8)
0 no	28 (100)	8 (73)	36 (82)
1 yes	0	0	0
Dose reduction			
NA	0	3 (27)	3 (8)
0	27 (96)	5 (46)	32 (82)
1	1 (4)	3 (27)	4 (10)
Retreatment postponed			
NA	0	3 (27)	3 (8)
0	24 (86)	6 (55)	30 (77)
1	4 (14)	2 (18)	6 (15)

NA, not available.

and every other cycle (at least one measurement was >1.5 cm). A reduction of at least 30% on two occasions 4 weeks apart defined a partial response; an increase of 20% over the nadir measurement was defined as progressive disease.[7] A complete response was defined as complete absence of all signs of disease without any new lesions or disease-related symptoms.

RESULTS

Patients Characteristics

Thirty-nine patients were enrolled from March 2004 until March 2006.Twenty-eight Danish patients received pemetrexed, three of these as third-line treatment and the others as second-line treatment. Eleven Norwegian patients received pemetrexed plus carboplatin as second-line treatment (Table 1). Most patients were men (90%), had epithelial subtype (85%), performance status of 0 to 1 (90%), and International Mesothelioma Interest Group stages III to IV (77%). Median age was 62 years (range, 30–77). Median lead times from initial diagnosis to start of study therapy were 283 days (range, 86–956) for pemetrexed and 389 days (range, 174–778) for pemetrexed plus carboplatin. This difference of 3.4 months in median is not statistically significant and may be due to stochastic variation, but may also reflect difficulties in getting resources for pemetrexed treatment to the Norwegian patients.

The previous chemotherapy regimens are shown in Table 1. Eleven patients (28%) had experienced objective tumor response to previous chemotherapy.

Toxicity

A total of 252 treatment courses were delivered, with a median of six (range, 1–23). Common Toxicity Criteria grade 3 or 4 toxicity occurred only with respect to leukopenia (14% with pemetrexed; 9% with pemetrexed plus carboplatin), thrombocytopenia (7% and 18%, respectively), and nausea (4% and 0%, respectively) (Table 2). There were no bleeding episodes, but one death due to sepsis with pemetrexed. This death occurred during the patient's third treatment course with both platelet and leukocyte count nadir of grade 4. The patient was admitted in poor clinical condition with high fever of 40.1°C and hypotension and died on the first day in hospital. There were no positive bacteriologic findings. Other less severe toxic effects of Common Toxicity Criteria grades 1 to 2 included tiredness (71% of patients), skin rash (32%), oral mucositis (15%), constipation (11%), and neurotoxicity (4%).

Dose was reduced in 4% of cases treated with pemetrexed and in 27% treated with pemetrexed plus carboplatin, and retreatment was postponed in 14% and 18%, respectively (Table 2). Postponements were not longer than 2 weeks.

Response and Survival

Partial responses rates were 21% with pemetrexed and 18% with pemetrexed and carboplatin. A progression-free survival curve is shown in Figure 1. Median times to progression were 147 days and 222 days, respectively, whereas median survival times were 294 days and 258 days (Table 3). An overall survival curve is shown in Figure 2. A total of 13 patients are alive, and the 1-year survival rate is 36% for both pemetrexed and pemetrexed plus carboplatin (Table 3).

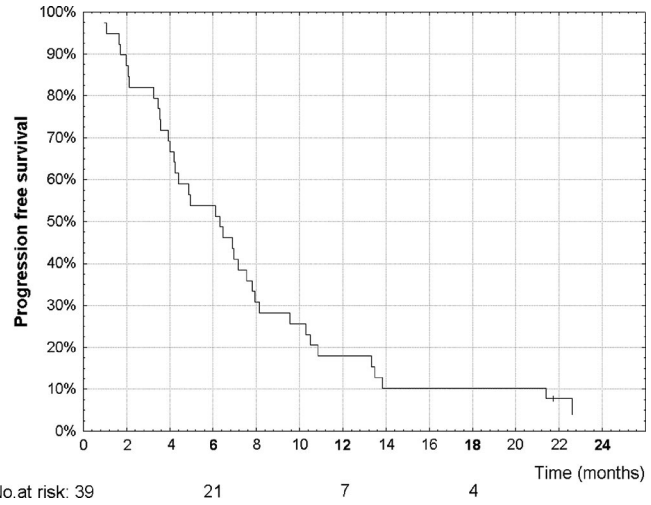

FIGURE 1. Progression-free survival for 39 patients with malignant pleural mesothelioma receiving second- or third-line treatment with pemetrexed alone ($n = 28$) or pemetrexed plus carboplatin ($n = 11$). Median progression-free survival was 6.1 months.

Partial responses occurred in two of 11 patients (18%) who responded to first-line treatment and in six of 23 patients without previous response (21%). One of three patients receiving pemetrexed as third-line treatment had partial response. These three patients had received vinorelbine plus cisplatin as first-line and gemcitabine plus liposomal doxorubicin plus carboplatin as second-line treatment. Two partial responses occurred with pemetrexed in five patients with the biphasic type and four of 22 patients with the epithelial subtype.

DISCUSSION

Platinum-based combination chemotherapy has been more efficacious than single-agent cisplatin in phase III trials, both with respect to the combination of pemetrexed and cisplatinum[6] and also raltitrexed plus cisplatinum.[8] Both of these randomized trials used antifolates and observed significantly prolonged survival with response rates and median survivals for the combinations of 41% and 12.1 months ($p = 0.02$) and 23.6% and 11.4 months ($p = 0.048$), respectively.[6,8] Based on these data, the combination of cisplatin with pemetrexed or raltitrexed can reasonably be offered as a first-line option in MPM. A number of other combination regimens using platinum compounds together with, for example, doxorubicin,[9] liposomal doxorubicin,[10] epirubicin,[11] gemcitabine,[12,13] and vinorelbine,[14] have also yielded promising results, although in nonrandomized studies. No randomized trials have as yet compared the efficacy of different combination chemotherapy regimens.[15] A number of patients treated with one of these regimens as first-line chemotherapy have a good performance status when progression of the disease is documented and inquire about second-line treatment. Because of the positive results obtained with antifolates as first-line treatment, these agents might be considered for second-line if the patients have not previously been exposed to this group of cytostatics. The current study indicates that

TABLE 3. Treatment Results with Pemetrexed in Malignant Pleural Mesothelioma Patients Previously Treated with Platinum-Based Combination Chemotherapy

Response	Pemetrexed (n = 28)	Pemetrexed + Carboplatin (n = 11)	Total (n = 39)
Partial, no. (%)	6 (21)	2 (18)	8 (21)
95% CI	8.3–40.9	2.3–51.8	9.3–36.5
No. of treatment courses			
1	2	0	2
2	3	1	4
3	1	2	3
4	2	1	3
5	2	1	3
6	8	1	9
7	0	1	1
8	6	0	6
9	4	2	6
20	—	1	1
23	—	1	1
Median (range)	6 (1–9)	6 (2–23)	6 (1–23)
Time to progression, d			
Median (range)	147 (30–644)	222 (50–898+)	183 (30–898+)
Survival, d			
Median (range)	294 (30–697)	258 (71–898+)	291 (30–898+)
Survival status			
Dead	18	8	26 (67%)
Alive	10	3	13 (33%)
1-yr survival	10 (36%)	4 (36%)	14 (36%)

CI, confidence interval.

such a strategy is justified and that a noteworthy rate of durable responses may be obtained.

Responses to pemetrexed were observed in patients previously treated with gemcitabine, liposomal doxorubicin, and vinorelbine. This indicates that there is no cross-resistance between these agents and pemetrexed. Such knowledge may be of potential use in the reverse situation, i.e., in patients who have received pemetrexed as part of the first-line treatment and who are considered for subsequent chemotherapy. The apparent absence of cross-resistance may further support the finding by Manegold et al.[16] that second-line chemotherapy after progression to pemetrexed plus cisplatin or cisplatin alone may possibly increase survival as patients who received subsequent second-line treatment survived longer than those who did not. However, there may be other explanations for the finding of a prolonged survival such as imbalances of known or unknown prognostic variables,[16] and firm conclusions regarding a survival effect by second-line treatment cannot be drawn.

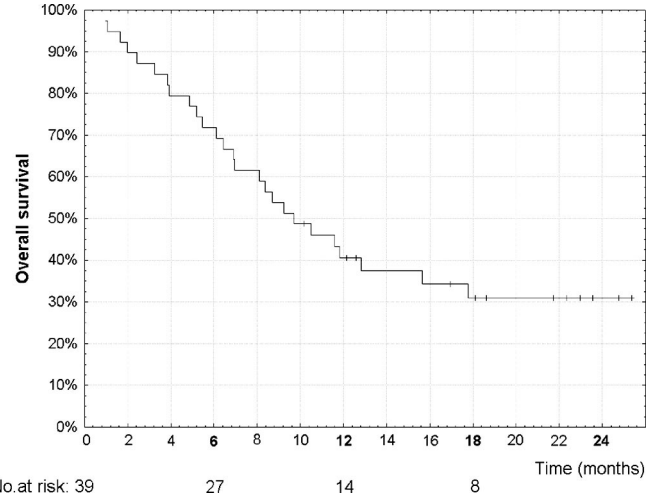

FIGURE 2. Overall survival for 39 patients with malignant pleural mesothelioma receiving second- or third-line treatment with pemetrexed alone (n = 28) or pemetrexed plus carboplatin (n = 11). Median overall survival was 9.7 months.

Although first-line chemotherapy in MPM is current standard of care,[17] fewer data are available concerning the role of second-line treatment or beyond. A literature review identified 16 trials on chemotherapy in previously treated MPM patients.[18] Partial response rates to a variety of agents were low, being 5% to 10% in many of these studies. A recent study evaluated a combination of raltitrexed plus oxaliplatin as second-line treatment.[19] Even though this combination is active in previously untreated patients, with response rates of 30% to 35%,[20] there were no responses among 14 patients pretreated with one of six chemotherapy regimens including doxorubicin, gemcitabine, pemetrexed, and methotrexate.[19]

This is contrast with the current study in which two of five patients who initially received gemcitabine plus carboplatin experienced partial responses to subsequent pemetrexed. Also two of 11 patients who initially received gemcitabine and carboplatin together with liposomal doxorubicin responded to subsequent pemetrexed plus carboplatin. This suggests a role for pemetrexed in second-line treatment of MPM.

The impact of histology on responsiveness to chemotherapy is well established, with the epithelial subtype being the most responsive to chemotherapy and having the best prognosis.[21] It is thus of interest that responses to second-line pemetrexed did occur also among patients having biphasic histology.

A recent phase II study of pemetrexed plus carboplatin in 19 chemotherapy-naive patients revealed a response rate of 18.6% and a median time to progression of 6.5 months.[22] These figures are similar to the results with an identical regimen used as second-line treatment in 11 patients in the current study (18.2% response rate and a median time to progression of 222 days [7.4 months]). It appears also similar to the results with pemetrexed alone in second-line treatment (21.4% response rate and a median time to progression of 147 days [4.9 months]) although the patients receiving the combination treatment had a trend toward more favorable prognostic factors than patients treated with pemetrexed alone, albeit not statistically significant. Increased myelotoxicity due to carboplatin may contribute to the lack of increased activity. It might thus be questioned whether carboplatin contributes to the activity of the combination in the second-line treatment setting if patients had been pretreated with carboplatin. This study cannot answer whether carboplatin is less active than cisplatin in MPM. The difference of 3.4 months in median lead time to pemetrexed treatment between the Danish and Norwegian patients is not statistically significant and may be due to stochastic variation, but may also reflect difficulties in getting resources for pemetrexed treatment to the Norwegian patients.

Another analysis of pemetrexed as second-line treatment in MPM based on data from an expanded access program was recently published.[23] A total of 187 pretreated patients received either pemetrexed alone (91 patients) or pemetrexed plus cisplatin (96 patients). The response rates were 32% for the combination of pemetrexed and cisplatin but only 5.5% for pemetrexed alone. The median survivals were 7.6 months for the combination and 4.1 months for the single agent. The Danish/Norwegian series differs in that the pemetrexed response rate was higher and the pemetrexed plus carboplatin response rate and median survival do not seem better than those with pemetrexed alone. However, given the nonrandomized nature of both data sets, it is possible that prognostic factor imbalances between the two groups in this study and that of Janne et al.[23] would account for the differences.

The influence of second-line chemotherapy on the clinical course of MPM remains unclear even though a reduction in tumor burden seems obtainable in some patients based on data from this and others studies. Whether this leads to an impact on survival and quality of life is as yet unproven and should be addressed in further trials. Preferably, a randomized trial of pemetrexed versus placebo should be conducted in this setting.

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