



Pemetrexed

(Alimta® - Eli Lilly)

by Jennifer Meudi, PharmD

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Malignant pleural mesothelioma (MPM) is an aggressive, highly lethal neoplastic disorder of the pleural lining of the lung associated with exposure to asbestos. In the United States, about 2,000 to 3,000 new cases of MPM are diagnosed annually.² Many cytotoxic agents, such as cisplatin, doxorubicin and gemcitabine, have been studied as single agents and in combinations in phase II trials. Results to date with conventional agents have been disappointing. Median survival in most single-agent studies has ranged from seven to nine months.³

Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer.⁴ For chemotherapy-naïve patients with a good performance status and stage IIIb or IV disease, platinum-based chemotherapy offers a modest survival advantage over best supportive care alone. Docetaxel was previously the only FDA-approved chemotherapy agent for the second-line treatment of advanced NSCLC. For patients with a good performance status at the time of disease progression following first-line chemotherapy, docetaxel, despite a low response rate, is associated with a 10 to 20% prolongation of one-year survival and an improved quality of life when compared to ifosfamide, vinorelbine or best supportive care alone in phase III studies.^{5,6}

PHARMACOLOGY

Pemetrexed is a multitargeted antifolate drug distinguished by a nucleus that differs from the core structures of other antifolates. Pemetrexed exhibits broad antitumor activity that targets at least three metabolic enzymes involved in both pyrimidine and purine synthesis. The major route for pemetrexed transport into tumor cells is the reduced folate carrier. The drug is metabolized rapidly in the cell to active polyglutamate derivatives that are potent inhibitors of enzymes critical to the synthesis of purines and thymidine. Long-term retention of the polyglutamated form of pemetrexed leads to persistently elevated intracellular concentrations and increased cytotoxic potential. This polyglutamated form has much greater affinity for thymidylate synthase than the parent compound. Because of this high affinity and long intracellular retention, pemetrexed may have greater clinical activity than other antifolates and thymidylate synthase inhibitors.³

The antitumor activity of pemetrexed is dependent on the size of cellular folate co-factor pools; therefore, toxicity increases with folate deficiency. When folates are abundant, toxicity is diminished and efficacy is optimized. Therefore, maintaining robust folate levels is critical to reducing toxicity and improving safety.³

Goal. The goal of this article is to provide the reader with information regarding pemetrexed and its use in the management of malignant pleural mesothelioma. This information should assist pharmacists optimize the care of patients receiving pemetrexed.

Objectives. 1) Describe the mechanism of action of pemetrexed and how it differs from other antifolates; 2) Review the studies that led to the approval of pemetrexed; 3) List the most common adverse effects associated with pemetrexed; 4) Describe some potential drug interactions with pemetrexed.

Summary

Indications. Pemetrexed in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.¹ Pemetrexed is also FDA-approved as a single-agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

Monitoring parameters. Complete blood counts, including platelet counts, should be performed on all patients receiving pemetrexed. Patients should be monitored for nadir and recovery before each dose, and on days 8 and 15 of each cycle. Periodic chemistry tests should be performed to evaluate renal and hepatic function.

Dose. The recommended dose for malignant pleural mesothelioma and non-small cell lung cancer is 500mg/m² as an intravenous infusion over 10 minutes on day 1 of each 21-day cycle. To reduce toxicity, patients must take a low-dose folic acid preparation or multivitamin with folic acid on a daily basis. Patients must also receive one intramuscular injection of vitamin B₁₂ during the week preceding the first dose of pemetrexed and every three weeks thereafter. Dose modifications should be made based on nadir hematologic counts or maximum non-hematologic toxicity from the preceding cycle of therapy as well as neurotoxicity.

Pediatrics. The safety and efficacy of pemetrexed in pediatric patients has not been established.

Geriatrics. Dose adjustments based on age are not necessary.

Renal insufficiency. Pemetrexed should not be administered if the creatinine clearance is <45 mL/min.

Hepatic Insufficiency. Data are unavailable as patients with a bilirubin of greater than 1.5 times the upper limit of normal (ULN) or transaminases greater than 3 times ULN were routinely excluded from clinical trials; patients with transaminases 3 to 5 times ULN were included if they had hepatic metastases. Patients experiencing any grade 3 or 4 non-hematologic toxicities (except grade 3 transaminase elevation or mucositis) should receive 75% of the previous pemetrexed dose upon initiation of the next cycle.

Pregnancy category. Category D

Breastfeeding. It is not known whether pemetrexed is excreted in human milk. It is recommended that nursing be discontinued if the mother is treated with pemetrexed.

Cost. Each 500 mg vial has an AWP of \$2,437.50.

TABLE 1. RESULTS FROM ANALYSIS OF EFFICACY PARAMETERS

	Intent to Treat		Fully Supplemented		Fully and Partially Supplemented	
	Arm 1 (n = 226)	Arm 2 (n = 222)	Arm 1 (n = 168)	Arm 2 (n = 163)	Arm 1 (n = 194)	Arm 2 (n = 184)
Survival						
Median, months	12.1	9.3	13.3	10.0	13.2	9.4
p-value	0.020		0.051		0.022	
Time to PD						
Median, months	5.7	3.9	6.1	3.9	6.1	4.3
p-value	0.001		0.008		0.003	
Tumor response						
Response rate, %	41.3	16.7	45.5	19.6	45.6	19.0
p-value	<0.001		<0.001		<0.001	

Arm 1= pemetrexed/cisplatin Arm 2= cisplatin

PHARMACOKINETICS

Pemetrexed is primarily excreted in the urine, with 70 to 90% of the dose recovered unchanged within the first 24 hours following administration. The elimination half-life of pemetrexed is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min). The clearance decreases, and area-under-the-curve (AUC) increases, as renal function decreases. Pemetrexed AUC and maximum plasma concentration increase proportionally with dose. The pharmacokinetics of pemetrexed do not change over multiple treatment cycles. In-vitro studies indicate that pemetrexed is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal impairment.¹

CLINICAL TRIALS

Malignant Pleural Mesothelioma

A multi-center, randomized, single-blind study was done by Vogelzang et al. to determine whether treatment with pemetrexed and cisplatin resulted in survival time superior to that achieved with cisplatin alone.⁷ Inclusion criteria specified histologically proven malignant pleural mesothelioma (MPM), age at least 18 years with life expectancy of at least 12 weeks, and a Karnofsky performance score of 70 or greater. Patients were excluded if they had received prior chemotherapy, had a secondary primary malignancy, or were unable to interrupt nonsteroidal anti-inflammatory drugs. The primary outcome was survival; with secondary outcomes of time to progressive disease,

time to treatment failure, tumor response rate, and duration of response also reported. Pemetrexed was administered intravenously (IV) at 500 mg/m² over 10 minutes, followed 30 minutes later by cisplatin 75 mg/m² IV over two hours on day 1 of a 21-day cycle. Those assigned to the cisplatin arm were treated likewise, except normal saline was given in the place of pemetrexed at an equivalent volume.

Three treatment deaths (7%) were reported among the first 43 patients randomly assigned to the experimental arm. Previous studies by Niyikiza et al had linked severe toxicities to high blood levels of homocysteine and methylmalonic acid at study entry, suggesting that such toxicity and possibly some deaths may be related to reduced folic acid and vitamin B₁₂ pools.⁸ Therefore, after 117 patients were enrolled, folic acid and vitamin B₁₂ (cyanocobalamin) supplementation was required for all patients receiving pemetrexed and for all of those subsequently enrolled. This resulted in three patient subgroups that were defined by supplementation status: 1) never supplemented patients who completed treatment prior to the implementation of protocol change (n = 70); 2) partially supplemented patients who began treatment prior to the protocol and completed treatment after the implementation (n=47); 3) fully supplemented patients who began treatment after the protocol (n =331).

The primary analysis of this study was performed on the population of all patients randomly assigned to treatment

who received study drug. An analysis was also performed on patients who received folic acid and vitamin B₁₂ supplementation during the entire course of therapy. Treatment arms were well balanced with respect to baseline characteristics. Patients were predominantly male and white, with a median age of 61 (range 19 to 85 years). Approximately two-thirds of the patients had epithelial histology, whereas 78% had stage III or stage IV disease.

Results from the analysis of efficacy parameters are summarized in Table 1. The median survival time for pemetrexed/cisplatin-treated patients was longer than for patients receiving cisplatin alone, 12.1 months and 9.3 months, respectively. In the fully supplemented subgroup, the median survival time was 13.3 months for the pemetrexed/cisplatin arm and 10.0 months in the control arm, representing a difference that is not statistically significant (p=0.051). Due to the small size of the partially supplemented subgroup (n=47), it was combined with the fully supplemented group (n=331) to explore the effect of treatment on the subgroup of patients who received supplementation at some time during therapy. In this subgroup, the survival time was similar between the pemetrexed/cisplatin and the cisplatin arms, 13.2 months and 9.4 months, respectively. The median time to progressive disease (PD) was significantly longer for patients who received pemetrexed/cisplatin as compared with cisplatin alone (5.7 months vs. 3.9 months; p=0.001). This difference

TABLE 2. GRADE 3 OR 4 TOXICITIES FROM PEMETREXED/CISPLATIN-TREATED PATIENTS

	Full Supplementation (n = 168)	Partial Supplementation + Never Supplemented (n = 58)	Full Supplementation + Partial Supplementation (n = 194)	No Supplementation (n = 32)
Hematologic laboratory toxicity				
Hemoglobin	7 (4.2%)	4 (6.9%)	8 (4.1%)	3 (9.4%)
Leukocytes	25 (14.9%)	15 (25.9%)	29 (14.9%)	11 (34.4%)
Neutrophils	39 (23.2%)	24 (41.4%)	51 (26.3%)	12 (37.5%)
Platelets	9 (5.4%)	4 (6.9%)	10 (5.2%)	3 (9.4%)
Non-laboratory toxicity				
Nausea	20 (11.9%)	13 (22.4%)	23 (11.9%)	10 (31.3%)
Fatigue	17 (10.1%)	6 (10.3%)	18 (9.3%)	5 (15.6%)
Vomiting	18 (10.7%)	12 (20.7%)	20 (10.3%)	10 (31.3%)
Diarrhea	6 (3.6%)	4 (6.9%)	7 (3.6%)	3 (9.4%)

was similar for the supplemented subgroup also (6.1 months vs. 4.3 months; $p=0.003$). The median time to treatment failure was also significantly longer in the pemetrexed/cisplatin arm than in the control arm. All responses seen were partial responses.

In the pemetrexed/cisplatin arm, grade 3 or 4 neutropenia (27.9%) and grade 3 or 4 leukopenia (17.7%) were the most common hematologic toxicities. In both treatment groups, nausea, vomiting and fatigue were the most commonly reported non-laboratory toxicities, with 88% of events reported as grade 3. Grade 3 or 4 toxicities from the pemetrexed/cisplatin groups are summarized in Table 2. The incidence of grade 3 or 4 neutropenia was significantly higher among the patients who were not supplemented or partially supplemented (41.4%), when compared to those that were fully supplemented (23.2%, $p=0.011$).

Non-Small Cell Lung Carcinoma

Hanna et al. conducted a randomized phase III trial to compare the efficacy and toxicity of pemetrexed versus docetaxel in patients with advanced NSCLC previously treated with chemotherapy.⁹ Eligible patients had a performance status 0 to 2, previous treatment with one prior chemotherapy regimen for advanced NSCLC, and adequate organ function. Patients received pemetrexed 500 mg/m² as a 10-minute intravenous infusion (n=283) or docetaxel 75 mg/m² IV over 1 hour

(n=288) on day one of a 21-day cycle. Patients in both arms were instructed to take dexamethasone, and patients receiving pemetrexed were supplemented with folic acid and vitamin B₁₂ throughout the trial. The primary endpoint was overall survival, with secondary objectives to compare toxicities, objective response rates, progression-free survival, time to progressive disease, time to treatment failure, time to response, duration of response, and quality-of-life measurements.

The two arms were well balanced for all demographic and stratification factors. The median number of cycles of chemotherapy administered was four in each

group, with a range of one to 20 and one to 14 for patients receiving pemetrexed and docetaxel, respectively. There was no significant difference in overall response rates (9.1% vs 8.8%) or stable disease rates (45.8% vs 46.4%) between the pemetrexed and docetaxel arms, respectively. There were no significant differences in progression-free survival, time-to-progression, time-to-treatment failure, median time to response, median duration of response, or median duration of clinical benefit. Table 3 summarizes the time-to-event variables. The one-year overall survival rate for each arm was 29.7%.

Overall, 472 patients (pemetrexed,

TABLE 3. SUMMARY OF TIME-TO-EVENT VARIABLES

Variable	Pemetrexed arm (n=283)	Docetaxel arm (n=288)	p-value
Progression-free survival (median, months)	2.9	2.9	0.759
Time-to-progression (median, months)	3.4	3.5	0.721
Time-to-treatment failure (median, months)	2.3	2.1	0.046
Duration of response (median, months)	4.6	5.3	0.427
Duration of clinical benefit (median, months)	5.4	5.2	0.450
Time-to-response (median, months)	1.7	2.9	0.105

TABLE 4. SELECTED GRADE 3 OR 4 TOXICITIES

	% of Pemetrexed patients (n = 265)	% of Docetaxel patients (n = 276)	p-value
Neutropenia	5.3	40.2	< 0.001
Febrile neutropenia	1.9	12.7	< 0.001
Neutropenia with infection	0.0	3.3	0.004
Anemia	4.2	4.3	0.99
Thrombocytopenia	1.9	0.4	0.116
Alopecia*	6.4	37.7	< 0.001
ALT	1.9	0	0.028
Fatigue	34	35.9	0.99
Nausea	30.9	16.7	0.57
Vomiting	16.2	12.0	0.72

*Alopecia= any grade. No alopecia in either group reported as grade 3 or 4.

TABLE 5. HOSPITALIZATIONS AND SUPPORTIVE CARE

	% of Pemetrexed patients (n = 265)	% of Docetaxel patients (n = 276)	p-value
≥ 1 hospitalization for neutropenic fever	1.5	13.4	< 0.001
≥ 1 hospitalization for any other drug-related adverse event	6.4	10.5	0.092
G-CSF/GM-CSF	2.6	19.2	< 0.001
Erythropoetin	6.8	10.1	0.169
RBC transfusions	16.6	11.6	0.108

TABLE 6. PEMETREXED DOSE REDUCTION BASED ON HEMATOLOGIC TOXICITIES

Nadir platelets > 50,000/mm ³ and nadir ANC < 500,000/mm ³	Administer 75% of previous dose
Nadir platelets < 50,000/mm ³ regardless of nadir ANC	Administer 50% of previous dose

TABLE 7. PEMETREXED DOSE REDUCTION BASED ON NON-HEMATOLOGIC TOXICITIES

Any Grade 3 or 4 toxicities except mucositis	Administer 75% of previous dose
Any diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea	Administer 75% of previous dose
Grade 3 or 4 mucositis	Administer 50% of previous dose

n = 239; docetaxel, n = 233) were evaluable for observer Lung Cancer Symptom Scale (LCSS) analysis. Patients in both arms were rated with similar rates of improvement or stabilization of anorexia (55.6% vs. 60.9%), fatigue (54.8% vs. 56.7%), cough (63.6% vs. 64.4%), dyspnea (63.6% vs. 59.9%), hemoptysis (70.3% vs. 73.2%) and pain (64.0% vs. 62.1%).

All 541 treated patients (n = 265 for pemetrexed, 276 for docetaxel) were assessable for response. Selected toxicities are summarized in Table 4. Required hospitalizations and supportive care are shown in Table 5. Patients receiving docetaxel experienced significantly higher rates of neutropenia, neutropenic fever, infections and hospitalization due to neutropenic events compared to patients receiving pemetrexed. In addition, the use of granulocyte colony-stimulating factors (G-CSFs) was substantially increased for patients receiving docetaxel when compared to pemetrexed. There were 49 patients who used G-CSF in the docetaxel arm and five in the pemetrexed arm for treatment of neutropenia or as prophylaxis for subsequent cycles following an episode of neutropenia. There were no statistically significant differences in the incidences of thrombocytopenia, anemia, RBC transfusions, or the use of erythropoetin between the treatment groups. There was a significantly higher rate of alopecia for patients receiving docetaxel, (6.4% vs. 37.7%, respectively (p<0.001)). There was a slightly higher incidence of rise in ALT for patients receiving pemetrexed.

Additionally, studies are being conducted to investigate the use of pemetrexed as a single agent in colorectal, breast, pancreatic, renal, and gastric cancers. Pemetrexed also continues to be studied in combination with other cytotoxic agents, including gemcitabine or carboplatin, in various malignancies.

DRUG INTERACTIONS

Pemetrexed should be used with caution when administering concurrently with ibuprofen, particularly in patients with mild to moderate renal insufficiency (CrCl from 45 to 79 mL/min). Daily ibuprofen doses of 400 mg four times daily have been shown to reduce pemetrexed clearance by about 20%. Avoid giving NSAIDs to all patients for at least five

days before, the day of, and two days following pemetrexed administration. If co-administration of an NSAID is necessary, closely monitor patients for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity. Co-administration of nephrotoxic drugs could result in delayed clearance of pemetrexed. Co-administration of substances that undergo tubular secretion (e.g., probenecid) could potentially result in delayed clearance of pemetrexed.¹⁰

ADVERSE EFFECTS

The most common hematologic toxicities associated with pemetrexed are neutropenia and thrombocytopenia. Dose adjustments for pemetrexed based on nadir ANC and platelets are outlined in Table 6.¹

If a patient develops non-hematologic toxicities (excluding neurotoxicity) \geq grade 3 (except grade 3 transaminase elevations), pemetrexed should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to guidelines in Table 7.

In the event of grade 3 or 4 neurotoxicity, patients should discontinue therapy. Pemetrexed should also be discontinued if a patient experiences any hematologic or non-hematologic grade 3 or 4 toxicity after two dose reductions.

MEDICATION SAFETY

The potential for medication errors with pemetrexed can mainly be attributed to storage, compounding and administration. When reconstituted, pemetrexed should be further diluted to 100 mL with 0.9% sodium chloride injection (preservative free) and administered as an infusion over 10 minutes. Pemetrexed should not be given IV push. Once diluted, pemetrexed is stable for up to 24 hours in the refrigerator. Pemetrexed is incompatible with diluents containing calcium, including Lactated Ringer's solution. Co-administration with other drugs and diluents has not been studied.¹

COST, DOSE AND HOW SUPPLIED

The recommended dose of pemetrexed is 500 mg/m² administered once every 21 days as an intravenous infusion. Pemetrexed is available in sterile single-use vials containing 500 mg. Pemetrexed should be stored at room temperature. An average dose for a patient would be approximately 1 gram IV every 21 days. The AWP is \$2,437.50 for a 500 mg vial. The average dose would cost approximately \$5,000 every 21 days.

CONCLUSION

As a new option for the management of malignant pleural mesothelioma,

pemetrexed should be considered for addition to the medication formulary in health systems that care for oncology patients. It is recommended that use be restricted to current labeled indications (including metastatic NSCLC). Poor third-party reimbursement for off-label indications should be expected, and coverage should be verified prior to initiation of therapy for all patients. ●

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QUIZ ANSWER FORM *circle one answer per question*

- | | | | | | | | |
|------|---|---|---|------|---|-----------|---|
| 1) A | B | C | D | 5) A | B | 9) A | B |
| 2) A | B | C | D | 6) A | B | C | D |
| 3) A | B | C | D | 7) A | B | C | D |
| 4) A | B | C | D | 8) A | B | C | D |
| | | | | | | 11) A | B |
| | | | | | | 12) A | B |
| | | | | | | 13) _____ | |

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March/April 2005
Pemetrexed (Alimta® - Eli Lilly)
 ACPE Universal Program Number: **175-000-05-038-H01**
 (No longer valid for CE credit after March 1, 2008)
 Release Date: March 1, 2005

SELF ASSESSMENT QUESTIONS

Pemetrexed (Alimta® - Eli Lilly)

1. Patients receiving pemetrexed must be supplemented with which of the following to reduce toxicities?
A. Folic Acid
B. Thiamine
C. Vitamin B₁₂
D. A & C
2. Which of the following statements is true?
A. Because of its high affinity and short intracellular retention, pemetrexed may have greater clinical activity than other antifolates and thymidylate synthase inhibitors.
B. Because of its low affinity and long intracellular retention, pemetrexed may have greater clinical activity than other antifolates and thymidylate synthase inhibitors.
C. Because of its high affinity and long intracellular retention, pemetrexed may have less clinical activity than other antifolates and thymidylate synthase inhibitors.
D. Because of its high affinity and long intracellular retention, pemetrexed may have greater clinical activity than other antifolates and thymidylate synthase inhibitors.
3. What is the approximate plasma protein binding of pemetrexed?
A. 81%
B. 70%
C. 90%
D. 35%
4. Which of the following statements is true regarding the clinical trial conducted by Vogelzang et al?
A. Median survival time was longer in patients receiving cisplatin alone than those receiving the combination of pemetrexed and cisplatin.
B. The median time to progressive disease was significantly longer for patients receiving the combination of pemetrexed and cisplatin than those receiving cisplatin alone.
C. The median time to treatment failure was significantly longer for patients receiving cisplatin alone than those receiving the combination of cisplatin and pemetrexed.
D. The median time to progressive disease was significantly longer for patients receiving cisplatin alone than those receiving the combination of pemetrexed and cisplatin.
5. The clinical trial conducted by Hanna et al showed an increased overall survival rate for the pemetrexed arm when compared to the docetaxel arm.
A. True
B. False
6. The trial comparing pemetrexed and docetaxel for non-small cell lung cancer showed a significantly lower rate of which of the following adverse effects associated with pemetrexed?
A. Anemia
B. Neutropenia
C. Thrombocytopenia
D. Fatigue
7. Which of the following medications may interact with pemetrexed?
A. Probenecid
B. Naproxen
C. Ibuprofen
D. All of the above
8. Which of the following pemetrexed dose adjustments needs to be made for grade 3 or 4 neurotoxicity?
A. Discontinue therapy
B. Administer 75% of the pemetrexed dose
C. Administer 50% of the pemetrexed dose
D. No adjustment necessary
9. Pemetrexed should be diluted in 100 milliliters of preservative free 0.9% sodium chloride and be administered as an infusion over 10 minutes.
A. True
B. False
10. When treating malignant pleural mesothelioma, pemetrexed should be given in combination with what other chemotherapeutic agent?
A. Docetaxel
B. Doxorubicin
C. Cisplatin
D. Gemcitabine
11. How do you rate this lesson?
A. Very Good
B. Good
C. Poor
12. Did it meet the learning objectives?
A. Yes
B. No
13. How long did it take you to complete this lesson?