National PBM Drug Monograph

Pemetrexed (Alimta®)

March 2005

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

- Pemetrexed is an antifolate that targets several enzymes involved with folate metabolism. It is a potent inhibitor of thymidylate synthase but a weaker inhibitor of dihydrofolate reductase and glycinamide ribonucleotide formyltransferase.
- Excretion is primarily renal as unchanged drug via glomerular filtration as well as tubular secretion. Adequate renal function (creatinine clearance ≥45 ml/min) is required for administration. NSAIDS and other drugs tubularly excreted should be avoided because of the potential for decreased clearance of pemetrexed.
- Clinical efficacy in malignant pleural mesothelioma was shown in a large phase III trial comparing pemetrexed plus cisplatin to cisplatin alone in patients with unresectable disease.
- The combination of pemetrexed and cisplatin resulted in a prolonged survival compared to cisplatin in malignant pleural mesothelioma, a disease highly resistant to chemotherapy.
- Adverse events in the pemetrexed arm were primarily hematologic. The incidence and severity of hematologic toxicities decreased in those patients who received vitamin supplementation from the start of therapy.
- Similar decreases in the incidence and severity of nausea, vomiting, stomatitis, and febrile neutropenia were seen in patients receiving vitamin supplementation.
- In non-small-cell lung cancer pemetrexed was compared to standard docetaxel as second-line therapy. Response rates, time to progressive disease, and survival were similar between the two arms.
- Survival rates may be compromised by the use of post-study chemotherapy in a higher percentage of patients on the pemetrexed arm.
- Pemetrexed was better tolerated with less neutropenia, less G-CSF use, less fever, less alopecia, and less hospitalizations than docetaxel.
- Pemetrexed patients experienced more days in the hospital, decreased creatinine clearance, increased transaminases, and more fatigue, anorexia, nausea, vomiting, and anemia than the docetaxel group.
- Increased homocysteine levels, indicating preclinical folate deficiency and increased methylmalonic acid, an indicator of B12 deficiency are associated with more toxicity from pemetrexed. All patients should receive folic acid and vitamin B12 throughout therapy.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating pemetrexed for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Synonyms: LY231514

Pharmacology/Pharmacokinetics[1,2]

Pemetrexed is a multitarget antifolate. Both the reduced folate carrier and membrane folate-binding protein transport system transport it into cells. Intracellularly, it is polyglutamated allowing for prolonged intracellular retention. Polyglutamated pemetrexed is approximately 60-fold more potent in inhibiting its primary enzyme target than the parent compound.

Polyglutamated pemetrexed inhibits multiple folate-dependent enzymes involved in purine and pyrimidine synthesis. The primary target is thymidylate synthase (TS), an enzyme involved in thymidine biosynthesis that is necessary for DNA synthesis. In addition, it is a weaker inhibitor of glycinamide ribonucleotide formyltransferase (GARFT), an enzyme involved in purine synthesis, and a very weak inhibitor of dihydrofolate reductase (DHFR), the enzyme required to reduce dihydrofolate to tetrahydrofolate which is generated in the synthesis of thymidylate by TS.

Mechanisms of resistance include decreased expression of the enzyme required for polyglutamation, increased activity of folylpolyglutamate hydrolase, and increased efflux by the multidrug resistance protein.

Table 1 Pemetrexed pharmacokinetics

Parameter	Pemetrexed values
Excretion	Renal (70-90% recovered unchanged)
Metabolism	Not to an appreciable extent. Does NOT inhibit CYP3A4, 2D6, 1A2, or 2C9
Half-life	3.5 hours with normal renal function
Plasma protein binding	81%

Special Populations:

Geriatrics: no effect of age on pharmacokinetics over a range of 26-80 years old

Pediatric: not included

Gender: no difference in pharmacokinetics between females and males

Race: pharmacokinetics were similar in Caucasians and African Americans; insufficient data in other ethnic groups

Hepatic Insufficiency: no effect from elevated AST, ALT, or total bilirubin; no studies in patients with hepatic impairment

FDA Approved Indication(s) and Off-label Uses

1. Mesothelioma- in combination with cisplatin for patients with malignant pleural mesothelioma whose disease in unresectable.

2. Non-small-cell lung cancer- as a single agent for patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

Current VA National Formulary Alternatives

Mesothelioma: There is no standard chemotherapy for mesothelioma. Numerous single-agents (doxorubicin, cisplatin, and methotrexate) and combinations have been used, but previous clinical trials were flawed due to study design, small prevalence of the disease, and lack of rigorous outcome measures.

Non-small-cell lung cancer: The current standard therapy for second-line therapy is single-agent docetaxel given on either an every 3-week schedule or on a weekly schedule.

Dosage and Administration

Mesothelioma:

Pemetrexed 500mg/m^2 as an intravenous infusion diluted in 100mL of 0.9% Sodium Chloride over 10 minutes on Day 1 of each 21-day cycle.

Plus

Cisplatin 75mg/m^2 as an intravenous infusion over 2 hours beginning approximately 30 minutes after the end of the pemetrexed infusion. Patients should be pretreated with antiemetics and hydration consistent with local practices.

Non-small-cell lung cancer:

Pemetrexed 500mg/m^2 as an intravenous infusion diluted in 100mL of 0.9% Sodium Chloride over 10 minutes on Day 1 of each 21-day cycle.

Premedication for pemetrexed:

Dexamethasone 4mg twice a day the day before, the day of, and the day after pemetrexed therapy reduces the incidence and severity of cutaneous reactions

Folic Acid 350-1000 mcg (the most common dose in clinical trials=400 mcg) at least 5 daily doses during the 7-days preceding the first dose of pemetrexed, then daily during therapy and for 21 days after the last dose of pemetrexed.

Give Vitamin B_{12} (cyanocobalamin) 1000mcg intramuscularly during the week before the first dose of pemetrexed and then every 3 cycles (every 9 weeks) thereafter. Dose may be administered on the same day as pemetrexed after the first dose.

(These reduce the incidence and severity of hematologic, gastrointestinal and mucosal adverse events)

Dose Reductions

Dose Reductions for Pemetrexed (single agent or in combination) and Cisplatin for Hematologic Toxicity

Nadir ANC <500ml/mm^3 and nadir platelets ≥50,000/mm^3	75% of previous dose (BOTH DRUGS)
Nadir Platelets <50,000/mm^3 regardless of nadir ANC	50% of previous dose (BOTH DRUGS)

Patients experiencing ≥Grade 3 nonhematologic toxicities should have pemetrexed held until resolution to less than or equal to pre-treatment value. (See next table)

Dose Reduction for Pemetrexed (single agent or in combination) and Cisplatin for Nonhematologic Toxicity[a]

Toxicity	Pemetrexed Dose	Cisplatin Dose
Any Grade 3 or 4 toxicity except mucositis[b]	75% of previous dose	75% of previous dose
Any diarrhea requiring hospitalization or any Grade 3 or 4 diarrhea	75% of previous dose	75% of previous dose
Grade 3 or Grade 4 mucositis	50% of previous dose	100% of previous dose

[a]Excluding neurotoxicity
[b]Except Grade 3 transaminase elevation

Dose Reduction for Pemetrexed (single agent or in combination) and Cisplatin for Neurotoxicity

CTC Grade	Pemetrexed Dose	Cisplatin Dose
0-1	100% of previous dose	100% of previous dose
2	100% of previous dose	50% of previous dose

Discontinuation: if patient experiences any grade 3 or 4 toxicity after 2 dose reductions (except grade 3 transaminase elevation) and immediately for any grade 3 or 4 neurotoxicity.

Elderly: No dose reductions required other than those above for patients ≥65 years old.

Renal Impairment: No dose reductions required other than those above in patients with a creatinine clearance ≥45 ml/min. Pemetrexed should not be administered to patients with a creatinine clearance less than 45 ml/min.

Hepatic Impairment: Pemetrexed is not extensively metabolized. Dose adjustments for hepatic insufficiency are given in the table above.

Efficacy

Efficacy Measures

Mesothelioma:
Primary: Survival
Secondary: Time to Progression, Response Rate, Pulmonary Function

Non-Small-Cell Lung Cancer:
Primary: Survival
Secondary: Time to Progression, Response Rate, QoL

Summary of efficacy findings

Mesothelioma:[3,4]

Phase II:

Results from a single phase II trial of 64 patients with unresectable disease who had not received prior chemotherapy were reported. Pemetrexed produced a 16.3% response rate and survival of 13 months in patients who were supplemented with folic acid and cyanocobalamin (see Adverse Events). Those who did not receive vitamin supplementation had a response rate of 9.5% and a survival of 8 months. Vitamin supplementation decreased toxicity and allowed for more pemetrexed to be administered. Adverse events were primarily hematologic.

Phase III:

Results from a phase III trial in 456 patients with unresectable disease who had not received prior chemotherapy were recently reported. This was the largest clinical trial ever conducted in pleural mesothelioma. Patients were randomized to pemetrexed plus cisplatin or cisplatin alone. Patients receiving pemetrexed plus cisplatin had a longer survival (12.1 months versus 9.3 months, p=0.02) and a longer time to progressive disease (5.7 months versus 3.9 months, p=0.001) when compared to cisplatin. Patients fully supplemented with vitamins had a survival of 13.3 months versus 10 months in the combination versus cisplatin alone arms, respectively (p=0.051). Response rates were higher in the combination arm (41.3% versus 16.7%). Second line chemotherapy was not controlled, and 37.6% of patients on the combination and 47.3% of patients on cisplatin alone received second-line chemotherapy.

Non-Small-Cell Lung Cancer:

Phase II: Second Line[5]

A phase II trial in 81 patients with progressive disease on first-line therapy or within 3 months after last chemotherapy was conducted using single-agent pemetrexed without vitamin supplementation. The response rate was 8.9%, median time to progression was 2 months, and median survival was 5.7 months. Adverse events were primarily hematologic and skin rash.

Phase III: Second Line[6]

Results from a large, phase III trial in previously treated patients compared single-agent pemetrexed to standard docetaxel therapy. The primary outcome measure was survival. Survival (8.3 months vs. 7.9 months), response rate (9.1% vs. 8.8%), stable disease (45.8% vs. 46.4%), and time to progression (3.4 months vs. 3.5 months) did not differ statistically between the pemetrexed arm and the docetaxel arm, respectively. Factors associated with increased survival included a PS of 0-1, stage IIIB disease, and a longer time since last chemotherapy. There was no difference between the arms with QoL parameters. On the pemetrexed arm, which included full vitamin supplementation, there was statistically significantly less grade 3 or 4 neutropenia, febrile neutropenia, neutropenia with infection, hospitalizations for neutropenia, and use of granulocyte colony-stimulating factor.

Phase II: First-line Therapy

Numerous pemetrexed phase II trials have been conducted in first-line therapy of non-small-cell lung cancer. The trials include single-agent pemetrexed as well as pemetrexed in combination with standard chemotherapy. Vitamin supplementation has mostly been absent. Reports of combination therapy with full vitamin supplementation have been reported in abstract form only. The number of patients in each trial is small. There appears to be some usefulness of pemetrexed in first-line therapy, although the best combination has yet to be determined. What is evident from these trials it the amount of hematologic toxicity that occurs without vitamin supplementation.

Pemetrexed Phase II Trials in Untreated Patients with NSCLC

Study	Dex	Vitamins	N	ORR	TTP	Survival	Select Grade3/4 toxicities
Rusthoven[7] Pemetrexed	Variable	N	30	23%	3.8 mo	9.2 mo	Neutropenia (39%), anemia (9%), thrombocytopenia (3%), feb neutropenia(12%), elevated bilirubin/AST (9-12%), rash (47.5% w/o dex, 12% w/dex)
Clarke[8] Pemetrexed	Variable	N	57	16%	4.4 mo	7.2 mo	Neutropenia (42%), anemia (10%), thrombocytopenia (5%), infection/fever (5%), elevated hepatic enzymes (24%), skin rash (31% w/o dex)
Shepherd[9] Pemetrexed/ Cisplatin	Yes	N	29	45%	NR	8.9 mo	Neutropenia (35%), anemia (19%), feb neutropenia ((3%), motor neuropathy (6%), stomatitis (3%)
Manegold[10] Pemetrexed/ Cisplatin	Yes	N	36	39%	6.3 mo	10.9 mo	Neutropenia (59%), anemia (14%), thrombocytopenia (17%), elevated bilirubin (3%), elevated AST ((3%), stomatitis (3%), motor neuropathy (6%)
Monnerat[11] Pemetrexed/ Gemcitabine	Yes	Variable	60	15.5%	5 mo	10.1 mo	Neutropenia (63%), anemia (12%), thrombocytopenia (5%), febrile neutropenia (15%)

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials*.

Adverse Events (Safety Data)[12]

Pemetrexed vs. Cisplatin (Fully Supplemented)

Adverse Event	CTC Grades % Incidence					
	Pemetrexed/Cisplatin (N=168)			Cisplatin (N=163)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hematologic						
Neutropenia	58	19	5	16	3	1
Leukopenia	55	14	2	20	1	0
Anemia	33	5	1	14	0	0
Thrombocytopenia	27	4	1	10	0	0
Renal						
Creatinine increase	16	1	0	12	1	0
Renal Failure	2	0	1	1	0	0
Constitutional						
Fatigue	80	17	0	74	12	1
Fever	17	0	0	9	0	0
Other	11	2	1	8	1	1
Cardiovascular						
Thrombosis/embolism	7	4	2	4	3	1
GI						
Nausea	84	11	1	79	6	0
Vomiting	58	10	1	52	4	1
Constipation	44	2	1	39	1	0
Anorexia	35	2	0	25	1	0
Stomatitis	28	2	1	9	0	0
Diarrhea	26	4	0	16	1	0
Dehydration	7	3	1	1	1	0
Dysphagia/esophagitis	6	1	0	6	0	0
Pulmonary						
Dyspnea	66	10	1	62	5	2
Pain						
Chest pain	40	8	1	30	5	1
Neurology						
Neuropathy/sensory	17	0	0	15	1	0
Mood alteration	14	1	0	9	1	0
Infection						
W/O neutropenia	11	1	1	4	0	0
W/neutropenia	6	1	0	4	0	0
Febrile neutropenia/Other	3	1	0	2	0	0
Febrile neutropenia	1	1	0	1	0	0
Immune						
Allergic/hypersensitivity	2	0	0	1	0	0
Dermatology						
Rash/desquamation	22	1	0	9	0	0

Pemetrexed vs. Docetaxel (Fully Supplemented)

Adverse Event	CTC Grades % Incidence					
	Pemetrexed (N=265)			Docetaxel (N=276)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hematologic						
Anemia	33	6	2	33	6	<1
Leukopenia	13	4	<1	34	17	11
Neutropenia	11	3	2	45	8	32
Thrombocytopenia	9	2	0	1	1	0
Hepatic/Renal						
ALT elevation	10	2	1	2	<1	0
AST elevation	8	<1	1	1	<1	0
↓Cr Clearance	5	1	0	1	0	0
Creatinine increase	3	0	0	1	0	0
Renal failure	<1	0	0	<1	0	0
Constitutional						
Fatigue	87	14	2	81	16	1
Fever	26	1	<1	19	<1	0
Edema	19	<1	0	24	<1	0
Myalgia	13	2	0	20	3	0
Alopecia	11	NA	NA	42	NA	NA
Arthralgia	8	<1	0	13	3	0
Other	8	1	1	6	1	<1
Cardiovascular						
Thrombosis/embolism	4	2	1	3	2	1
Ischemia	3	2	1	2	<1	0
GI						
Anorexia	62	4	1	58	7	<1
Nausea	39	4	0	25	3	0
Constipation	30	0	0	23	1	0
Vomiting	25	2	0	19	1	0
Diarrhea	21	<1	0	34	4	0
Stomatitis/pharyngitis	20	1	0	23	1	0
Dysphagia/esophagitis	5	1	<1	7	1	0
Dehydration	3	1	0	4	1	0
Pulmonary						
Dyspnea	72	14	4	74	17	9
Pain						
Chest pain	38	6	<1	32	7	<1
Neurology						
Neuropathy/sensory	29	2	0	32	1	0
Mood alteration	11	0	<1	10	1	0
Infection						
W/O neutropenia	23	5	<1	17	3	1
Feb neutropenia/other	6	2	0	2	<1	0
Febrile neutropenia	2	1	1	14	10	3
W/neutropenia	<1	0	0	6	4	1
Immune						
Allergic/hypersensitivity	8	0	0	8	1	<1
Dermatologic						
Rash/desquamation	17	0	0	9	0	0

Common Adverse Events

The five most common adverse events are fatigue, anorexia, nausea, dyspnea, and anemia.

Serious Adverse Events- Non-Small Cell Lung Cancer Trial

Event	Pemetrexed (N=265) %	Docetaxel (N=276) %	P-value
Dyspnea	4.9	9.1	0.065
Febrile neutropenia	1.5	11.2	<0.001
Pneumonia	6.8	5.1	
Pyrexia	4.5	3.6	
Anemia	3.8	2.5	
Neutropenia	0.0	6.2	<0.001
Asthenia	1.5	2.9	
Pleural effusion	0.4	2.2	
Abdominal pain	2.3	0.0	0.013

Tolerability[13]

Early trials with pemetrexed and other antifolates revealed severe and cumulative toxicities such as myelosuppression, diarrhea, and mucositis that became life-threatening. A multivariate analysis of data from these early trials was performed to identify variables that predicted for toxicity. The analysis found that elevated homocysteine levels predicted preclinical folate deficiency and resulted in a more severe toxicity profile that included neutropenia, thrombocytopenia, severe diarrhea, and mucositis. In addition, elevated levels of methylmalonic acid, a marker for vitamin B12 deficiency, were found to be predictors of severe diarrhea and mucositis. The current clinical data in which patients were supplemented with folic acid and cyanocobalamin found that severe toxicities were greatly reduced without compromising efficacy.

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 14).

Precautions/Contraindications

Precautions

Skin rash has been reported more frequently in patients not pretreated with dexamethasone.

The effect of third-space fluids, like pleural effusions or ascites, on pemetrexed pharmacokinetics has not been thoroughly investigated. Consideration should be given to draining the fluid prior to pemetrexed administration.

The use of pemetrexed in patients with a creatinine clearance <45 ml/min has been insufficiently studied. Pemetrexed should not be administered to patients with a creatinine clearance <45 ml/min.

Pregnancy Category D: Pemetrexed has been shown to be fetotoxic and teratogenic in mice. It has not been studied in pregnant women; advise patients to avoid pregnancy during therapy.

Nursing Mothers: It is not know if pemetrexed enters breast milk. Because of the potential harm to infants, advise mothers to discontinue nursing during pemetrexed therapy.

Contraindications

Pemetrexed is contraindicated in anyone with a history of severe hypersensitivity reaction to pemetrexed or any of the components in its formulation.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

This section must contain the following paragraph:

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name pemetrexed: A-methapred, Penetrex, trimetrexate, ceftriaxone, Cetapred, Emetrol, medipred, Merrem, methotrexate

LA/SA for trade name Alimta: Alinia, Elimite, Aceta, Adalimumab, Alfenta, Esclim

Potential problems include trimetrexate and methotrexate that have similar names and similar dose forms and vial strengths, although doses are not exact. This poses a moderate risk for error. Do not store Alimta next to trimetrexate or methotrexate.

Drug Interactions

Drug-Drug Interactions

Pemetrexed is eliminated unchanged in the urine as the result of glomerular filtration and tubular secretion. Administration with nephrotoxic drugs could delay clearance of pemetrexed. Concomitant administration with drugs that are tubularly secreted may delay clearance of pemetrexed.

NSAIDS: Although pemetrexed has been administered with ibuprofen (400mg four times a day maximum) in patients with normal renal function (creatinine clearance >80ml/min), caution should be used when used concurrently in patients with mild to moderate renal insufficiency (creatinine clearance 45-79 ml/min). It is advised that patients avoid NSAIDS with short elimination half-lives for 2 days before, the day of, and for 2 days after pemetrexed administration. There is no data on concurrent use with NSAIDS with long elimination half-lives. Patients taking NSAIDS with long elimination half-lives should interrupt therapy for 5 days before, the day of, and for 2 days after pemetrexed therapy.

Acquisition Costs

Drug	Dose	Cost/cycle/patient ($)	Cost/4 cycles/patient ($)
Pemetrexed $1441.60/vial	500mg/m^2	$2883.20	$11,532.80
Docetaxel 100mg=$754.23 20mg= $185.81	75mg/m^2	$1311.66	$5,246.64

Pharmacoeconomic Analysis

There are no pharmacoeconomics analyses available for this product.

Conclusions

Clinical Efficacy

Mesothelioma: Treatment of mesothelioma with standard chemotherapy drugs rarely produces response rates above 20%. Most clinical trials have been small phase II trials with multiple design flaws including inadequate pathologic diagnosis and staging and vague response criteria. Survival has generally been in the 6-8 month range. Measurement of tumor response in this disease can be difficult, even using serial CT scans which is now the standard because the disease grows in sheets rather than spheres. The FDA limited outcomes measures to survival.

In the largest clinical trial in malignant pleural mesothelioma, pemetrexed plus cisplatin was compared to cisplatin alone in patients with unresectable disease. The combination resulted in a significantly better overall survival (12.1 months versus 9.3 months). Second-line chemotherapy could have skewed survival estimates in favor of the control arm, but survival in the combination therapy arm was still statistically better. Pulmonary function tests, lung capacity, and QoL studies have not been reported yet.

Non-small-cell lung cancer: Numerous combination chemotherapy regimens exist for first-line therapy of non-small-cell lung cancer. For older patients or those with a poor performance status, some single-agent therapies have also been studied. Response rates to chemotherapy tend to decrease with each subsequent line of therapy. Second-line therapy should be considered for patients with good performance status. Docetaxel was the only chemotherapy agent with an FDA indication for second-line therapy.

In a large, randomized clinical trial pemetrexed was compared to docetaxel as second-line therapy for non-small-cell lung cancer. Survival, objective response rate, and time to progression of disease did not differ significantly between the two arms. Pemetrexed was associated with significantly less fever, neutropenia, hair loss, neuropathy, and hospitalizations. However, pemetrexed patients spent more days in the hospital, had significantly higher increases in transaminases, increased serum creatinine, skin rash, fatigue, nausea, anorexia, vomiting, and weight loss. A limitation to the study includes the use of post-study chemotherapy. Post-study chemotherapy was used in 46.6% of pemetrexed patients and 37.2% of docetaxel patients. Analysis found that patients receiving any kind of post-study chemotherapy survived longer, calling into question the survival reported for the pemetrexed arm.

Safety

With full vitamin supplementation, the severe toxicities from pemetrexed are reduced without compromising efficacy. Specifically, hematologic and gastrointestinal toxicities are most affected by vitamin supplementation and are rarely greater than Grade 3. In non-small-cell lung cancer patients who received full vitamin supplementation, pemetrexed was better tolerated than docetaxel in second-line therapy, requiring fewer hospitalizations, less use of granulocyte colony stimulating factor, and fewer episodes of infection. (See table)

Hospitalizations and Supportive Care- NSCLC

Outcome	Pemetrexed	Docetaxel	P-value
Hospitalizations-Admissions	337	364	
Study Drug Admissions	123	151	
Adverse Events (all)	113	147	
Febrile Neutropenia	4	43	<0.001
Other Drug Related	17	29	
Non Drug Related	92	75	
Protocol Tests	72	49	
Social Reasons	29	17	
Hospitalizations-Days	1722	1410	
Study Drug Admissions	314	314	
Adverse Events (all)	885	833	
Febrile Neutropenia	29	195	
Other Drug Related	131	151	
Non Drug Related	725	487	
Protocol Tests	143	100	
Social Reasons	380	163	
G-CSF/GM-CSF	2.6%	19.2%	<0.001

Recommendations

Mesothelioma:

With no other current standard chemotherapy regimen for malignant pleural mesothelioma, the increased survival data from the large phase III trial establishes the combination of pemetrexed plus cisplatin with full vitamin supplementation as the new standard of care for patients with unresectable disease.

Criteria for use in mesothelioma include: unresectable disease without brain metastases, good performance status (e.g. ECOG PS 0-2), adequate renal function (creatinine clearance >45 ml/min), not taking NSAIDS, able to comply with the vitamin supplementation regimen.

Non-small cell lung cancer:

Until recently, docetaxel was the only drug with an FDA indication for second-line therapy of non-small-cell lung cancer. Traditionally, second-line therapy has produced poor results. In a large phase III trial, pemetrexed produced response rates, time to progression, and survival similar to docetaxel but with less toxicity and presumably less resource utilization. The drug was approved based on response rate, since survival analysis did not show superiority or non-inferiority compared to docetaxel and survival data was colored by the use of post-study chemotherapy by a higher percentage of patients in the pemetrexed arm. Nonetheless, near equivalent response rates (a surrogate endpoint) and less toxicity (with less resource utilization) make this an attractive alternative for second-line therapy. Its exact place in therapy is unknown, especially with erlotinib recently receiving approval for use after failure of one prior chemotherapy regimen. However, many patients are now receiving docetaxel (or paclitaxel) as a first-line agent, making pemetrexed an important alternative for second-line therapy.

Criteria for use in non-small cell-lung cancer: Stage IIIB or IV NSCLC without brain metastases, one prior chemotherapy regimen, adequate renal function (creatinine clearance >45 ml/min), not taking NSAIDS, no pleural effusion or third-spacing of fluid, good performance status (e.g. ECOG PS 0-2), able to comply with the vitamin supplementation regimen.

References:

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to August 2004) using the search terms pemetrexed and mesothelioma and non-small cell lung cancer. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. Medical Review transcripts from the FDA website for the indication in mesothelioma were reviewed. All randomized controlled trials (phase III) and controlled trials (phase II) published in peer-reviewed journals were included.

Table 1. Pemetrexed in Mesothelioma.

Trial	Eligibility Criteria	Interventions	Patient Population Profile	Study Endpoints	Efficacy Results
Scagliotti 2003 Phase II MC, SC	Inclusion criteria 1.Histologic diagnosis of MPM 2.Not surgical candidate 3. Measurable disease 4. PS≥70 Karnofsky Exclusion criteria 1. Prior systemic chemo 2. Brain metastases 3. Inability to interrupt NSAID therapy	Pemetrexed 500mg/m^2 in 100ml NS over 10 min Q3 weeks Folic Acid: 350-1000mcg PO daily, start 1-2 weeks before therapy and throughout study Vitamin B_{12} 1000mcg intramuscularly, start 1-2 weeks before therapy, then every 9 weeks Dexamethasone 4mg twice daily the day before, day of, and day after therapy No salicylates or NSAID Leucovorin for grade 4: neutropenia, leukopenia or thrombocytopenia lasting ≥5 days	Characteristic: ALL (n=64) % male: 82.8 Age(yrs): 65 (39-80) PS 70: 10.9% 80: 32.8 90: 50 100: 6.3 Stage I: 6.3% II: 7.8 III: 34.4 IV: 51.6	Primary: Tumor Response Secondary: Duration of response Survival TTP TTF QoL PFT changes	Primary Endpoint

Primary Endpoint

Population	Response rate %	95% CI	No. of responders CR	PR	No. with SD as best response	Total number of patients
Investigators:						
Supplemented	16.3	6.8-30.7	0	7	27	43
Non-suppl.	9.5	1.2-30.4	0	2	6	21
All	14.1	6.6-25	0	9	33	64
Independent Reviewer:						
Supplemented	17.1	7.2-32.1	0	7	28	41
Non-supple.	20	4.3-48.1	0	3	9	15
All	17.9	8.9-30.4	0	10	37	56

Time to Event

Event	Median Time to Event (months)	95%CI
Survival	10.7	7.7-14.5
Supplemented	13	8.5-∞
Nonsupplemented	8	4.8-14.5
TTP	4.7	4.2-5.8
Supplemented	4.8	4.4-6.1
Nonsupplemented	3	1.7-5.8
TTF	4.4	3.1-5.5
Duration of response (N=9)	8.5	4.4-12.7

Adverse Events
Grade 3/4 neutropenia 23.4%
Grade 3/4 leukopenia 18.8
Grade 3/4 neutropenia
Supplemented 9.3
Nonsupplemented 52.4
Grade 4 chest pain (nonsupplemented) 1 patient
Grade 3 chest pain
Supplemented 10/21 patients
Nonsupplemented 15/43 patients

Trial: Vogelzang 2003 Phase III MC, R, SB

Eligibility Criteria

Inclusion criteria:
1. Histologic diagnoses MPM
2. Not surgical candidate
3. Measurable disease
4. PS≥70 Karnofsky

Exclusion criteria:
1. Prior chemotherapy
2. Secondary 1°malignancy
3. Brain metastases
4. Unable to stop NSAID therapy

Interventions

I:
Pemetrexed 500mg/m^2 in 100ml NS over 10 min
Followed by
Cisplatin 75mg/m^2/2hrs
Repeat every 21 days

Folic Acid: 350-1000mcg PO daily, start 1-3 weeks before therapy and throughout study

Vitamin B_{12} 1000mcg intramuscularly, start 1-3 weeks before therapy, then every 9 weeks

Dexamethasone 4mg twice daily the day before, day of, and day after therapy

No salicylates or NSAID

II:
Cisplatin 75mg/m^2/2hrs
Repeat every 21 days

Patient Population Profile

Charac-teristic	Arm1 N=226	ARM II N=222
%male	81.4	81.5
Age		
Mean	60	60
range	29-85	19-84
Race		
% white	90.3	92.8
%PS		
70	16.4	14
80	31.9	29.7
90/100	51.8	56.3
Stage		
I	7.1	6.3
II	15.6	15
III	32.4	30.9
IV	45.1	48.2

Study Endpoints

Primary:
Survival

Secondary:
TTP
TTF
Response Rate
Duration of response (pulmonary function, QoL, lung density reported elsewhere)

Efficacy Results

Time to Event

Event	ITT P/C (226)	ITT C (222)	Fully S P/C (168)	Fully S C (163)	Full+Partial S P/C (194)	Full+Partial S C (184)
Survival						
Median (mos)	12.1	9.3	13.3	10	13.2	9.4
95%CI	10-14.4	7.8-10.7	11.4-14.9	8.4-11.9	10.9-14.8	8.4-11.6
Hazard Ratio	0.77		0.75		0.71	
Log rank P	0.02		0.051		0.022	
TTP						
Median (mos)	5.7	3.9	6.1	3.9	6.1	4.3
95%CI	4.9-6.5	2.8-4.4	5.3-7	2.8-4.5	5.4-6.7	3-4.9
Hazard Ratio	0.68		0.64		0.7	
Log rank P	0.001		0.008		0.003	
Tumor response (PR)						
Response %	41.3	16.7	45.5	19.6	45.6	19
Fisher's P	<0.001		<0.001		<0.001	

Adverse Events
Most common grade 3/4 toxicity:
Pem/Cisplatin neutropenia 27.9% (greater in NS vs. PS/FS group)
Leukopenia 17.7%

N,V,fatigue grade 3 in ≥88%

FS group had less toxicity overall except for dehydration

MC=multicenter, SC=single cohort, R=randomized, SB=single-blind, MPM=malignant pleural mesothelioma, PS=performance status, NSAID=non-steroidal antiinflammatory drug, PO=oral, TTP=time to progressive disease, TTF=time to treatment failure, QoL=quality of life, PFT=pulmonary function tests, CR=complete response, PR=partial response, SD=stable disease ; S=supplemented; FS=fully supplemented; PS=partially supplemented;P/C=pemetrexed plus cisplatin; C=cisplatin; N=nausea; V=vomiting

Table 2. Pemetrexed in Non-Small-Cell Lung Cancer.

Trial	Eligibility Criteria	Interventions	Patient Population Profile	Study Endpoints	Efficacy Results
Hanna 2004 Phase III R, MC Support by Eli Lilly	Inclusion criteria: 1.histologic or cytologic NSCLC stage III or IV 2.1 prior chemo for advanced disease 3.Measurable disease 4.ECOG PS 0-2 5. adequate BM, renal, hepatic fxn Exclusion criteria: 1.Prior docetaxel or pemetrexed 2.≥grade 3 peripheral neuropathy 3.unable to stop NSAID therapy 4.uncontrolled pleural effusion 5.symptomatic or uncontrolled brain mets 6.significanct weight loss (≥10% BW in 6 seeks)	I: Pemetrexed 500mg/m^2 in 100ml NS over 10 min Q21 days Folic Acid: 350-1000mcg PO daily, start 1-2 weeks before therapy and throughout study, continue until 3 weeks after last dose Vitamin B_{12} 1000mcg intramuscularly, start 1-2 weeks before therapy, then every 9 weeks Dexamethasone 4mg twice daily the day before, day of, and day after therapy II: Docetaxel 75mg/m^2 over 1 hour Q21 days Dexamethasone 8mg twice a day the day before, day of, and day after therapy	See table below	Primary: Overall survival Secondary: Toxicity comparison Obj Response Rate PFS TTP Duration of response QoL (LCSS)	See table below

Charac-terstic	Pem (283)	Doc (288)
Male%	68.6	75.3
Age Median Range	 59 22-81	 57 28-87
PS 0-1 2	 88.6% 11.4	 87.6% 12.4
Prior Platinum	92.6%	89.9%
Time since last chemo <3mos	50.4%	48.1%
Prior paclitaxel	25.8%	27.8%

Results	Pemetrexed	Docetaxel
Response rate %	9.1	8.8
Stable disease %	45.8	46.4
Response rate if: CR/PR to 1st line SD on 1st line PD on 1st line	 11.1% 10.2 4.6	
SD if: CR/PR to 1st line SD on 1st line PD on 1st line	 47% 50 40.3	
Overall survival (median mos)	8.3	7.9 (p=0.226)
TTP (median mos)	3.4	3.5
TTF (median mos)	2.3	2.1
Duration of response (median mos)	4.6	5.3

Factors associated with increased survival: PS 0 or 1, stage Ii disease, longer time since last chemotherapy

QoL: no difference between the arms in rates of improvement of anorexia, fatigue, cough, dyspnea, hemoptysis, and pain

Adverse Events:

Grade 3 or 4 Hematologic Toxicity

Toxicity	% Pem patients	% Docetaxel patients	P
Neutropenia	5.3	40.2	<0.001
Febrile Neutropenia	1.9	12.7	<0.001
Neutropenia W/infection	0.0	3.3	0.004
Thrombocytopenia	1.9	0.4	0.116

Trial	Eligibility Criteria	Interventions	Patient Population Profile	Study Endpoints	Efficacy Results

Hospitalizations or Supportive Care

Outcome	% Pem patients	% Docetaxel patients	p
≥1 hosp. For neutropenic fever	1.5	13.4	<0.001
≥1 hosp. For other drug related AE	6.4	10.5	0.092
Growth factor use	2.6	19.2	<0.001
Epoetin	6.8	10.1	0.169
RBC transfusion	16.6	11.6	0.1078
Alopecia	6.4	37.7	<0.001
ALT	7.9	1.4	0.028

Smit 2003
Phase II
MC

Group A:
Disease progression or recurrence following platinum-based therapy

Group B:
Disease progression or recurrence following treatment without platinum

Grant from

Inclusion criteria:
1.WHO PS 0-1
2.Stage IIIB or IV NSCLC
3.PD on 1st line therapy or w/I 3 months after last chemo
4.measurable disease
5.adequate organ function

Exclusion criteria:
1.brain metastases
2. active infection
3. pregnancy
4. breast feeding
5. serious systemic disorder
6. detectable effusions

Pemetrexed 500mg/m^2 in 100ml NS over 10 min Q21 days

Dexamethasone 4mg twice daily the day before, day of, and day after therapy

No NSAIDS starting 2 days before therapy and continuing until 2 days after each infusion

Character-stic	Total (81)
Age	
Mean	61
Range	32-80
WHO PS	
0	20
1	59
Stage	
IIIB	14
IV	65
1st-line chemo	
Cisplatin	29
Carboplatin	15
Gemcitabine	28
Vinorelbine	25
Mitomycin	19
Paclitaxel	10
Docetaxel	8
Time since last chemo	
≤1 month	52
1-2 months	16
≥2 months	11

Primary:
Response rate

Secondary:
Duration of response
TTP
TTF
Survival

Response	All% (79)	GroupA% (44)	GroupB% (35)
CR	1.3	0	2.9
PR	7.6	4.5	11.4
SD	32	36	26
PD	38	41	34
No assessment	22	18	26

Overall response rate 8.9%

Event	All	Group A	Group B
Med survival	5.7	6.4	4
Duration of response	2	1.6	6.8
TTP	2	2.3	1.6

Adverse Events

Hematologic parameter	Grade 3 %	Grade 4%
Hemoglobin	12	1
WBC	30	9
Neutrophils	16	19
Platelets	10	5

Trial	Eligibility Criteria	Interventions	Patient Population Profile	Study Endpoints	Efficacy Results
Eli Lilly			Best response to 1st-line chemo CR 0 PR 20 SD, 31 PD 28		
First-line Data					
Clarke 2002 Phase II MC	Inclusion criteria: 1.Stage III or IV NSCLC 2. measurable disease 3.No prior chemotherapy 4. adequate organ function Exclusion criteria: 1. pregnant or breast feeding 2.active infection 3. serious concomitant disorder 4. brain mets requiring steroids 5.Clcr <45ml/min 6. clinically detectable third space fluid	Pemetrexed 600mg/m^2 in 100ml NS over 10 min Q21 days Dexamethasone 4mg twice daily the day before, day of, and day after therapy if grade 2 or greater skin toxicity No NSAIDS starting 3 days before therapy	Charac-teristic: % patients (59) Med Age 59 Range 39-74 %Male 66 Stage IIIA 10 IIIB 24 IV 66 PS 0 20 1 48 2 32	Primary: Response rate Secondary Survival	Response / No. of patients (%) PR 9 (15.8) SD 27 (47) Median duration of response: 4.9 months Median TTP: 4.4 months Median Survival: 7.2 months Adverse Events Grade 3 or 4 Event / % patients Neutropenia 42 Infection 3 (only grade 3) Thrombocytopenia 5 Leukopenia 34 Cutaneous 31 Nausea 14 (grade 3 only) Vomiting 8
Rusthoven 1999 Phase II MC Supported by NCIC and Eli Lilly	Inclusion criteria: 1.Stage III or IV NSCLC 2.measurable disease 3.Adjuvant chemo allowed if last dose was ≥12 months earlier 4. ECOG PS 0-2	Pemetrexed 600mg/m^2 in 100ml NS over 10 min Q21 days No NSAIDS or salicylates on or around the day of treatment	Charac-teristics: No. of patients (33) Age Mean 63 Range 42-74 Males 26 PS 0 13 1 19	Primary: Response Rate Secondary: Response duration	Outcome / No. of patients (%) (30 evaluable) PR 7 (23.3) Median TTP: 3.8 months (0.5 – 15.8) Median Survival: 9.2 months Higher response was seen in patients with stage III disease

Trial	Eligibility Criteria	Interventions	Patient Population Profile	Study Endpoints	Efficacy Results
	5.normal renal and hepatic function 5. adequate BM reserve Exclusion criteria: 1. third spacing of fluid 2. brain metastases 3. no concurrent treatment with other investigational drugs, chemotherapy, or folic acid supplements		2: 1 Stage III: 8 IV: 25		
Manegold 2000 Phase II MC Sponsored by grant from Eli Lilly	Inclusion criteria: 1.StageIIIb or IV NSCLS 2. measurable lesions 3.No prior chemo; XRT to less than 25% BM 4.PS 0-1 WHO 5.adequate BM reserve 6.adequate renal and hepatic function Exclusion criteria: 1.active infection 2. CNS metastases 3. third-spacing of fluid 4. albumin <2.5 5. unable to interrupt ASA or NSAID therapy	Pemetrexed 500mg/m^2 in 100ml NS over 10 min Q21 days Cisplatin 75mg/m^2 administered per local protocol with pre- & post-hyrdration every 21 days Dexamethasone 4mg twice daily the day before, day of, and day after therapy	Charac-Terstic: Percent patients (36) Age Median: 58 Range: 26-73 Male: 81 PS 0: 22 1: 75 Stage IIIB: 50 IV: 50 Prior treatment None: 80 Surgery: 17 XRT: 3	Primary: Response rate Secondary: Duration of response TTP Survival	Outcome / Percent patients / 95%CI PR: 39: 23-57 SD: 47 Time to Event Event / Months / 95%CI Duration of response: 10.4: 0.3-15.4 TTP: 6.3: (2.9-14.1) Survival: 10.9: 6.8-16.9 Median number of cycles per patient: 4 (1-11) Adverse Events: Hematologic Tox / Grade 3 % / Grade 4% Granulocytopenia: 28: 31 Anemia: 14: 0 Thrombocytopenia: 14: 3 Non-hematologic toxicity / Grade 3% / Grade 4% Nausea/vomiting: 6: 0 Diarrhea: 3: 3 Neuromotor: 6: 0 Pulmonary: 3: 0

Trial	Eligibility Criteria	Interventions	Patient Population Profile	Study Endpoints	Efficacy Results
					Stomatitis: 3 / 0 Increased bilirubin: 3 / 0 Increased AST: 3 / 0 Increased ALT: 0 / 3
Shepherd 2001 Phase II MC Supported in part by grant from Eli Lilly to NCIC	Inclusion criteria: 1. Stage IIIB or IV NSCLS 2. no prior therapy 3. measurable disease 4.prior XRT if acute side effects resolved and not given to sole sight of disease 5. PS 0-2 ECOG 6. adequate blood counts 7. serum creatinine WNL of institution Exclusion criteria: 1. Brain metastases 2. prior chemotherapy 3. unable to interrupt ASA or NSAID therapy	Pemetrexed 500mg/m^2 over 10 minutes Cisplatin 75mg/m^2 over 60 minutes with mannitol diuresis according to institutional standards Dexamethasone 4mg PO twice a day the day before, day of, and for 6 doses after treatment Every 21 days	Charac-teristic / No. of patients (31) Age Median: 60 Range: 35-75 Male: 11 PS 0: 2 1: 24 2: 5 Stage IIIB: 5 IB: 26	Primary: Response rate Secondary: Duration of response Survival	Outcome / Percent patients PR: 45 (95%CI 26-64) Duration of response Median: 6.1 months Range: 1.6-7.8 months Survival Median: 8.9 months Range: 1-15+ 1-year survival: 49 Median number of cycles per patient: 6 Adverse Events: Hematologic Toxicity / Grade 3 No. of patients / Grade 4 No. of patients Anemia: 5 / 1 Leukocytopenia: 5 / 2 Neutropenia: 7 / 4 Thrombocytopenia: 0 / 1 Infection: 0 / 0 Febrile neutropenia: 1 / 0 Non-hematologic toxicity / Grade 3 No. of patients / Grade 4 No. of patients Fatigue: 8 / 0 Anorexia: 1 / 0 Nausea: 1 / 0 Vomiting: 1 / 0 Diarrhea: 2 / 1 Stomatitis: 1 / 0 Neuromotor: 2 / 0
Monnerat 2004 Phase II	Inclusion criteria: 1. stage IIIB or IV NSCLC	Gemcitabine 1250mg/m^2 over 30 minutes D 1 and 8	Charac-teristic / No. (%) (60) Age	Primary: Response rate	Outcome / Percent patients / 95%CI PR: 15.5 / 7.3-27.5 SD: 50

Trial	Eligibility Criteria	Interventions	Patient Population Profile	Study Endpoints	Efficacy Results
MC Supported by a grant from Eli Lilly	2. measurable disease 3. significant effusion needed to drained and pleurodesis performed at least 2 weeks prior 4. PS 0-1 WHO 5. Cl_{CR} ≥45ml/min 6. adequate hepatic function, BM function 7. absence of >10% weight loss is past 6 weeks Exclusion criteria: 1. prior chemotherapy or XRT to target lesions 2.serious concomitant illness 3. secondary primary tumor 4. brain metastases	Pemetrexed 500mg/m^2 in 100ml NS over 10 minutes On D 8 90 minutes after gemcitabine Dexamethasone 4mg twice a day the day before, day of, and day after pemetrexed Folic Acid: 350-1000mcg PO daily, start 1-2 weeks before therapy and throughout study Vitamin B_{12} 1000mcg intramuscularly, start 1-2 weeks before therapy, then every 9 weeks No ASA or NSAID starting 2 days before, day of, and 2 days after pemetrexed	Median 58 Range 34-73 Male 38 (63.3) PS 0 20 (33.3) 1 40 (66.7) Stage IIIB 8 (13.3) IV 52 (86.7)	Secondary: Survival PFS Duration of response	PD 20.7 Not evaluated 13.8 Time to Event / Months / 95%CI Survival 10.1 7.9-13 PFS 5 3.5-6.3 Duration of response 3.3 2.7-7.1 57% of patients received subsequent post-study chemotherapy Lung Cancer Symptom Score: Highest rates of improvement: anorexia, cough, pain Highest rates of worsening: fatigue Adverse Events:

Hematologic Toxicity	Grade 3 No. of patients	Grade 4 No. of patients
Anemia	7	0
Leukopenia	21	4
Neutropenia	17	20
Febrile neutropenia	8	1
Thrombocytopenia	3	0

Non-hematologic Toxicity	Grade 3 No. of patients	Grade 4 No. of patients
Rash	2	0
Fatigue	14	0
Anorexia	1	0
Nausea	0	0
Vomiting	0	0
Stomatitis	1	0
Pneumonitis	2	1
Increased AST	8	1
Increased ALT	9	3
Increased Bilirubin	0	1

R=randomized, MC=multicenter, NSCLC=non-small cell lung cancer, BM=bone marrow, BW=body weight, PFS=progression-free survival, TTP=time to progression, TTF=time to treatment failure, QoL=quality of life, PD=progressive disease, CR=complete response, PS=partial response, SD=stable disease, XRT=radiation therapy;