

Brief Report



The Effectiveness of Pemetrexed in the Treatment of Mesothelioma

<i>Reviewer</i>	<i>Melissa Carter</i>
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Important Note:

- ***The purpose of this brief report is to summarise information on the effectiveness of pemetrexed in the treatment of mesothelioma and to provide best practice advice.***
- ***It is not intended to replace clinical judgement, or be used as a clinical protocol.***
- ***A reasonable attempt has been made to find and review papers relevant to the focus of this report, however it does not claim to be exhaustive.***
- ***This document has been prepared by staff of the Evidence Based Healthcare Advisory Group, ACC. The content does not necessarily represent the official view of ACC or represent ACC policy.***
- ***This report is based upon information supplied up to October 2004.***
- ***An application has been made to Pharmac to fund pemetrexed. At the completion of this report, the outcome of the application was unknown.***

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Executive Summary

Malignant Pleural Mesothelioma (MPM) is an uncommon malignancy, often caused by exposure to asbestos (50-70% of cases¹). Mesothelioma is the classic tumour associated with asbestos exposure, and has a latency period of 20-40 years or more from the time of first exposure.² Once a person is diagnosed with mesothelioma, their prognosis is often extremely poor, with a life expectancy of between 6 to 18 months (5-year survival <5%).¹ Until recently, no treatments have been shown to be able to cure this disease or extend life expectancy.

In August 2004, a new drug called pemetrexed (brand name ALIMTA®) was registered for use in New Zealand for the treatment of malignant pleural mesothelioma in combination with cisplatin.

Objectives

To investigate the amount and range of information available which examines the effectiveness of pemetrexed in treating mesothelioma, and if possible, determine the effectiveness, safety and cost-effectiveness of pemetrexed in the treatment of mesothelioma.

Search

A number of medical databases were searched using the key words “pemetrexed” and “mesothelioma.” Results were limited to “human” and had to be written in the English language.

Selection Criteria

Randomised controlled trials, systematic reviews, meta-analyses, case-control studies and case series which examined the effectiveness of pemetrexed in the treatment of malignant pleural mesothelioma (MPM) were included. Papers written in a language other than English, abstracts and non-systematic reviews were excluded from the analysis.

Data Collection and Analysis

All studies that fitted the above criteria were obtained and appraised by the principal investigator using the Scottish Intercollegiate Guidelines Network (SIGN) grading system³ (see Appendix 4) to determine the levels of evidence. The type of study and study quality were determined by reviewing the methodology of each study.

Main Results

One randomised controlled trial (level 1+ evidence) and two case series' (level 3 evidence) were found which examined the effectiveness of pemetrexed in the treatment of mesothelioma.

Reviewers' Conclusions

Pemetrexed 500mg/m² given in combination with cisplatin 75mg/m² given every 21 days appears to be effective in extending life expectancy by an average of 3 months for patients with mesothelioma. Pemetrexed + cisplatin should be given in combination with given with folic acid and vitamin B₁₂ to reduce the toxicity of the drugs.

Background

Malignant Pleural Mesothelioma (MPM) is an uncommon malignancy, often caused by exposure to asbestos (50-70% of cases¹). Asbestosis refers to scarring in the lungs caused by the inhalation of asbestos fibres and is generally regarded as a disease likely to occur from significant and prolonged exposure to asbestos.² Mesothelioma is the classic tumour associated with asbestos exposure, and has a latency period of 20-40 years or more from the time of first exposure.² The median age of onset is 50-60 years.

In New Zealand, the number of mesothelioma cases amongst women has remained fairly constant over recent years at a rate of 1.3 per million per annum.⁴ Amongst men, however, the annual rate rose from around 4.3 per million (7 cases) in 1985 to 18.2 per million (31 cases) in 1992.⁴ In 2000, there were 56 deaths in New Zealand due to all types of mesothelioma, and 62 deaths in 2001 (NZHIS provisional data). Of the 56 deaths in 2000, 44 were mesothelioma of the pleura (ICD code C450). The majority of these deaths were in men (88.6%), with all deaths occurred in people over the age of 50 years. A similar pattern is observed within the cancer registry data for 2000.

Once a person is diagnosed with mesothelioma, their prognosis is often extremely poor, with a life expectancy of between 6 to 18 months (5-year survival <5%).¹ Until recently, no treatments have been shown to be able to cure this disease or extend life expectancy. An increase of 6 weeks in survival is considered to be a clinically significant improvement in terms of cancer medications [personal communication, Carolyn Cameron, Eli Lilly and Company].

In August 2004, a new drug called pemetrexed (brand name ALIMTA®) was registered for use in New Zealand for the treatment of malignant pleural mesothelioma in combination with cisplatin. Pemetrexed acts by attacking multiple enzyme targets, namely dihydrofolate reductase, thymidylate synthase (TS), and glycinamide ribonucleotide formyl transferase.⁵

A request was put forward by Sunita Goyal (Pharmaceutical Advisor, Healthwise) in September 2004 to investigate the effectiveness of pemetrexed in the treatment of mesothelioma.

Objectives

- To investigate the amount and range of information available which examines the effectiveness of pemetrexed in treating mesothelioma, including any cost-effectiveness information.
- To determine the effectiveness, safety and cost-effectiveness of pemetrexed in the treatment of mesothelioma.

Methods

Investigation

A literature search was undertaken on September 6th 2004 utilising the following medical databases:

- Ovid MEDLINE 1966-August Week 4 2004
- Ovid MEDLINE daily update 1-9-04
- EMBASE 1988-2004 week 35
- ACP Journal Club 1991 to March/April 2004
- CCTR 2nd Quarter 2004
- CDSR 2nd Quarter 2004
- DARE 2nd Quarter 2004

Key words and terms used were “pemetrexed” and “mesothelioma.” Results were limited to “human” and had to be written in the English language (see Appendix 3 for the search strategy).

The reference lists of all articles included in this review, as well as the reference lists of all articles listed in the table of excluded studies (see Appendix 2) were hand searched.

The Medsafe Datasheet⁶ was obtained and searched for references. A representative from Eli Lilly (the pharmaceutical company who market and supply Alimta®) also provided a list of references which was searched for further articles relevant to this review.

Types of studies included in the review

Randomised controlled trials, systematic reviews, meta-analyses, case-control studies and case series which examine the effectiveness of pemetrexed in the treatment of malignant pleural mesothelioma (MPM).

Exclusion criteria: Papers written in a language other than English. Papers were also excluded if they were only available as an abstract, including conference proceedings.

All studies that fitted the above criteria were obtained and appraised by the principal investigator using the Scottish Intercollegiate Guidelines Network (SIGN) grading system³ (see Appendix 4) to determine the levels of evidence.

The type of study and study quality were determined by reviewing the methodology of each study. Each of the following aspects of each study were analysed: condition for which pemetrexed was being investigated, other drugs being used in combination with pemetrexed, inclusion and exclusion criteria for participants, sample size, blinding, randomisation, withdrawal rates, amount of follow-up, outcome measurements, and potential bias in the study. Evidence tables were created which summarised this information as well as the outcomes and level of evidence.

Results

The literature search resulted in 604 “hits” of which 183 included the word “pemetrexed” in the title. This list was reduced to 30 once the titles and abstracts had been skimmed.

Original Articles

One key article was found which was referenced in the majority of other articles. This was a randomised controlled trial (Vogelzang et al 2003⁷) which investigated the effectiveness of pemetrexed in combination with cisplatin versus cisplatin alone in patients with mesothelioma. Two further case series⁷ were also found which met the inclusion criteria.

The randomised controlled trial showed that patients who were given pemetrexed 500mg/m² + cisplatin 75mg/m² had a median survival time of 2.8 months longer than those who were given placebo + cisplatin⁷ (p<0.05). Forty-one percent of patients in the

intervention group responded to the treatment compared with 16.7% in the control group (p<0.001). Part way into the trial, folic acid and vitamin B₁₂ were also given to all patients to improve the side effect profile, and once added, there was a significant reduction in toxicity in the intervention group. The most common side effects of the pemetrexed/cisplatin combination were found to be nausea (14.6%), vomiting (13.3%), and diarrhoea (4.4%)⁷.

In the case series by Scagliotti et al 2003⁵, 14.1% of patients given pemetrexed 500mg/m² responded to the treatment. Folic acid and vitamin B₁₂ were also given to improve patient safety.

In the second case series by Hughes et al 2002⁸, patients were given pemetrexed and carboplatin at a range of concentrations between 400-500mg/m² for pemetrexed, and 4mg/mL-min to 6mg/mL-min carboplatin. Thirty-two percent of patients responded to this treatment combination.⁸

Non-systematic Reviews

Seventeen non-systematic reviews were found which examined the effectiveness of pemetrexed, either alone or in combination with cisplatin, for the treatment of mesothelioma. Due to the large number of non-systematic reviews, and relatively few studies, these reviews have been summarised below in Table 1. These studies were classified as non-systematic reviews as the methodology was not described in adequate detail to allow another researcher to replicate the study.

All seventeen reviews concluded that pemetrexed was effective in the treatment of mesothelioma.

TABLE 1: Summary of non-systematic reviews of the effectiveness of pemetrexed in the treatment of mesothelioma

<i>Article</i>	<i>Title</i>	<i>Conclusions</i>	<i>Effective?</i>
Adjei, A 2003 ⁹ [Source of funding not stated]	Pemetrexed (Alimta): A novel multitargeted antifolate agent	Pemetrexed/cisplatin combinations show remarkable efficacy in mesothelioma. Pemetrexed is an agent that is convenient to administer (10 min infusion every 3 weeks) and with vitamin supplementation has a mild toxicity profile. It remains to be seen if the broad activity of this agent will be maintained in all tumour types with vitamin supplementation.	Yes
Bischoff, HG et	Pemetrexed (ALIMTA): a	Pemetrexed and cisplatin supplemented with	Yes

al 2002 ¹⁰ [Source of funding not stated]	new effective drug in chemotherapy of malignant pleural mesothelioma (MPM)	FA/B12 should now be considered standard treatment for patients with non-resectable MPM.	
Boyer, M 2002 ¹¹ [Dr Boyer has received honoraria from Eli Lilly and Company]	Pemetrexed: single-agent and combination phase I study overview	Pemetrexed is a novel and well-tolerated cytotoxic agent that has been evaluated in a series of phase I trials. Phase II and III studies are now under way.	Yes
Budde, L and N Hanna 2004 ¹² [Source of funding not stated]	Pemetrexed (Alimta): improving outcomes in malignant pleural mesothelioma	Pemetrexed/cisplatin delays time to progression of disease and improves overall survival. Improvements in pulmonary function testing and quality of life were also observed. Vitamin supplementation of pemetrexed is imperative as it significantly reduces side effects.	Yes
Catalano, A et al 2003 ¹³ [Funded by the Associazione Italiana per la Ricerca sul Cancro (AIRC) and the Italian Ministero dell'Università e della Ricerca Scientifica (ex 60%) to A. Procopio]	Experimental therapy of malignant mesothelioma: New perspectives from anti-angiogenic treatments	The combination pemetrexed and cisplatin has demonstrated superior median overall survival, response rate, lung function and quality of life measures in the largest randomised trial in MM.	Yes
Fossella, F and U Gatzemeier 2002 ¹⁴ [Dr Fossella and Gatzemeier have received research grant support and honoraria from Eli Lilly and Co.]	Phase I Trials of Pemetrexed	Pemetrexed clearly is a promising drug. It seems to have activity against a broad range of cancers, including those that are not particularly sensitive to chemotherapy, such as malignant pleural mesothelioma.	Yes
Gadgeel, S and H Pass 2004 ¹⁵ [Source of funding not stated]	Novel combinations using pemetrexed in malignant mesothelioma	Recent data has suggested that pemetrexed is an effective drug in the treatment of malignant mesothelioma, particularly in combination with cisplatin. Vitamin supplementation with folic acid and vitamin B ₁₂ is essential to reduce adverse effects of pemetrexed.	Yes
Green, M 2002a ¹⁶ [Source of funding not stated]	The evolving role of gemcitabine and pemetrexed (Alimta) in the management of patients with malignant	Several single agents have demonstrated clinical activity in mesothelioma. There is no individual agent or combination that remains the unquestioned standard for first-line treatment, and exploratory phase II trials of new single agents	Yes

stated]	mesothelioma	remain ethical. Within the past 5 years, several studies have demonstrated that gemcitabine and pemetrexed are active, both as single agents and in combination, in patients with mesothelioma.	
Green, M 2002b ¹⁷ [Source of funding not stated]	Alimta (pemetrexed disodium): A multitargeted antifolate for the treatment of mesothelioma	Pemetrexed disodium combined with B ₁₂ and folate vitamin supplementation has demonstrated single-agent activity against malignant mesothelioma.	Yes
Hanauske, A-R 2004 ¹⁸ [Source of funding not stated]	The role of Alimta in the treatment of malignant pleural mesothelioma: An overview of preclinical and clinical trials	Alimta is a new generation multi targeted antifolate antimetabolite and has demonstrated clinical activity in several solid human malignancies. It administration is easy and convenient. Alimta is safe and effective both as single agent and in various combinations. Supplementation with folic acid and Vitamin B ₁₂ further reduces Alimta-related side effects.	Yes
Harrison T and L Scott 2003 ¹⁹ [Source of funding not stated]	Pemetrexed	In a first-line setting in chemotherapy-naïve patients with advanced MPM, pemetrexed plus cisplatin prolonged median survival time by 3 months in a phase III trial, and this combination treatment was generally well tolerated in patients receiving supplementation with folic acid and cyanocobalamin.	Yes
Kindler, H 2004 ²⁰ [Source of funding not stated]	The Emerging Role of Pemetrexed for the Treatment of Malignant Mesothelioma	Pemetrexed plus cisplatin is the first chemotherapy combination that has been demonstrated to improve survival in patients with malignant mesothelioma.	Yes
Manegold, C 2003 ²¹ [Source of funding not stated]	Pemetrexed (Alimta, MTA, multitargeted antifolate, LY231514) for malignant pleural mesothelioma.	The EMPHACIS trial, the first phase III randomised study in mesothelioma with survival as the primary study end point, showed statistically significant superiority of the cisplatin/pemetrexed combination over cisplatin alone for overall survival, progression-free survival, response rate, lung function improvement, and reduction of tumor-induced symptoms.	Yes
Maung, K 2002 ²² [Source of funding not stated]	Pemetrexed (Alimta): a novel antifolate in the treatment of malignant pleural mesothelioma	Single-agent pemetrexed is active in the treatment of mesothelioma. A significant improvement in survival was observed in patients treated with pemetrexed/cisplatin compared to patients treated with cisplatin alone. The pemetrexed/cisplatin combination should be considered the new standard for the management of advanced malignant mesothelioma.	Yes
Paz-Ares, L et al 2003 ²³ [L Paz-Ares and H Cortes-Funes have given lectures with honorarium paid by Eli	Review of a Promising New Agent – Pemetrexed Disodium	Pemetrexed disodium is a new and multitargeted antifolate that exhibits significant anti-tumour activity in a wide range of solid tumours, including NSCLC, mesothelioma, and carcinomas of the breast, colon, uterine cervix, head and neck, and bladder.	Yes

Lilly and Company]			
Suwanrusme, H et al 2004 ²⁴ [Source of funding not stated]	Pemetrexed Alone and in Combination with Platinum Compounds in the Management of Malignant Mesothelioma	Pemetrexed, a multitargeted antifolate (MTA), showed promising activity as a single agent or in combination with platinum agents in 3 different phase I/II trials. The combination of cisplatin/pemetrexed is now a data-driven choice for first line therapy in patients with MPM.	Yes
Tomek, S and C Manegold 2003 ²⁵ [Source of funding not stated]	Chemotherapy for malignant pleural mesothelioma	In the largest randomised MPM trial, pemetrexed in combination with cisplatin was shown to improve median overall survival, pulmonary function, and quality of life measures. These data indicate that systemic therapy with pemetrexed and cisplatin may soon emerge as a standard for this aggressive disease.	Yes

Discussion

Pemetrexed is the first drug known to prolong survival in patients with Malignant Pleural Mesothelioma (MPM). Although pemetrexed has been registered for use in New Zealand since August 2004, pemetrexed is not currently funded or subsidised, although it is readily available at full cost. An application has been put forward by Eli Lilly to Pharmac to fund pemetrexed, however, to date, the outcome of this application is unknown. Until such a decision has been made, some analysis of its effectiveness is required to assist the Corporate Medical Advisor in making funding decisions for ACC claimants. ACC has already been approached to fund pemetrexed, and has 30-40 mesothelioma claimants per year.

Review of the published literature shows that the vast majority of the literature around pemetrexed cites the randomised controlled trial by Vogelzang et al⁷ which shows its effectiveness in improving survival of patients with MPM. This study found a 41% increase in survival in patients receiving the pemetrexed/cisplatin combination compared to patients receiving cisplatin alone. Given the disease's poor prognosis, this is a significant breakthrough in treatment.

There is currently no information in the literature on the cost-effectiveness of pemetrexed + cisplatin in the treatment of mesothelioma. The current purchase price of pemetrexed is \$2241 per vial (GST exclusive). For a 70kg patient, approximately two vials would be infused at each treatment time [personal communication, Carolyn Cameron, Eli Lilly and Company]. Cisplatin is an extra \$143.80 per cycle. Eli Lilly has recommended that if a

person does not respond to pemetrexed + cisplatin after two cycles, then it is probably not worth continuing with the treatment [personal communication, Carolyn Cameron, Eli Lilly and Company]. However, currently there is no limit to the number of cycles that a patient may receive.

The pemetrexed + cisplatin combination recommended treatment programme does appear to have a number of unpleasant side effects, most commonly nausea (14.6%)⁷ and vomiting (13.3%).⁷ These side effects need to be weighed against the symptoms of the disease and poor prognosis. However, folic acid and vitamin B₁₂ appear to reduce the incidence of side effects.

Conclusions

Pemetrexed 500mg/m² given in combination with cisplatin 75mg/m² every 21 days appears to be effective in extending life expectancy by an average of 2.8 months for patients with mesothelioma. Pemetrexed + cisplatin should be given in combination with folic acid and vitamin B₁₂ to reduce the toxicity of the drugs.

Pemetrexed + cisplatin appears to have minimal side effects, the most common of which appear to be nausea and vomiting.

There appears to be no information in the literature regarding the cost-effectiveness of pemetrexed.

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APPENDIX 1: Summary of Results of the Effectiveness of Pemetrexed

Study	Methods	Participants	Intervention	Outcomes	Comments and level of evidence
<p>Vogelzang, NJ et al 2003⁷</p> <p>[Funded by Eli Lilly and Company]</p>	<p>Randomised controlled trial.</p> <p>Multicentre, single-blind (patients only), random assignment.</p> <p>Primary outcome was survival which was defined as the time from randomisation to the time of death from any cause.</p> <p>After 117 patients had enrolled, folic acid and vitamin B12 were added to reduce toxicity.</p>	<p>456 patients with malignant pleural mesothelioma who were chemotherapy naïve and not eligible for curative therapy.</p> <p>Mean age 60.5 years Age range 19-85 years 18.3% female 90% white</p> <p>226 Intervention Group 222 Control Group</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Uni or bi-dimensionally measurable disease • Age ≥18 years • Life expectancy ≥12 weeks • Karnofsky performance status ≥70 <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Prior chemotherapy • Second primary malignancy 	<p><u>Intervention Group:</u> Pemetrexed 500mg/m² IV over 10 minutes, then 30 minutes later Cisplatin 75mg/m² IV over 2 hours. Repeated every 21 days.</p> <p><u>Control Group:</u> Saline IV over 10 minutes, then 30 minutes later Cisplatin 75mg/m² IV over 2 hours. Repeated every 21 days.</p>	<p>Median survival time in intervention group was 12.1 months versus 9.3 months in the control group (p=0.020). Median time to disease progression was significantly longer in the intervention group: 5.7 versus 3.9 months (p=0.001).</p> <p>Response rates were 41.3% in intervention group and 16.7% in control group (p<0.0001).</p> <p>Once folic acid and vitamin B12 were added, there was a significant reduction in toxicity in the intervention group.</p> <p>Median follow-up was 10 months.</p> <p>In both groups, nausea, vomiting, and fatigue were the most commonly reported toxicities with ≥88% of events reported as Grade 3. The incidence of nausea (14.6% vs 6.3%), vomiting (13.3% vs</p>	<p>Level 1+</p> <p>3 treatment related deaths (7%) were reported among the first 43 patients randomly assigned to the intervention group.</p>

		<ul style="list-style-type: none"> Brain metastases Unable to interrupt NSAIDs[#]. 		3.6%), diarrhoea (4.4% vs 0%), dehydration (4.0% vs 0.5%) and stomatitis (4.0% vs 0%) were all significantly higher in the intervention group (p<0.05).	
Scagliotti, GV et al 2003 ⁵ [Source of funding not stated]	Clinical study – case series. Multicentre (10 clinics in Germany, Italy, UK and USA).	<p>64 patients with a histologically proven diagnosis of MPM, chemotherapy-naïve measurable lesions, and adequate organ function.</p> <p>Median age 65 years Age range 39-80 years 17.2% female</p> <p>Most patients had a diagnosis of epithelioid pleural mesothelioma at either stage III or IV. Two patients (3.1%) had prior radiotherapy, and 30 patients (46.9%) had prior surgery.</p>	<u>Intervention:</u> Pemetrexed 500mg/m ² IV over 10 minutes every 3 weeks. After a protocol change, most patients also received folic acid and vitamin B12 supplementation to improve safety.	<p>9/64 (14.1%) patients had a partial response. Median overall survival was 10.7 months.</p> <p>43/64 patients received vitamin supplementation. 7/9 responders were vitamin-supplemented. The median overall survival was 13 months for supplemented and 8 months for non-supplemented patients. Vitamin-supplemented patients completed more cycles of therapy than non-supplemented patients (median 6 vs 2 cycles).</p> <p>Grade 3/4 neutropenia (23.4%) and grade 3/4 leukopenia (18.8%) were the most common toxicities.</p> <p>There were 23 reports of serious adverse events in the study. 7 patients had adverse events that resulted in withdrawal from the</p>	Level 3

[#] ALIMTA® Data Sheet: Clinical trials have shown a decrease in pemetrexed clearance following administration of ibuprofen. It is recommended that patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives at least 2 days prior to, and on the day of, and at least 2 days after administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt for at least 5 days before, on the day of, and at least 2 days after pemetrexed administration. If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity.

				study. Six patients only completed one cycle, and one patient completed 20 cycles.	
Hughes, A et al 2002 [*] [Source of funding not stated]	Clinical study – case series.	27 patients with MPM. Median age 58 years Age range 39-78 years. 14.8% female. <u>Inclusion criteria:</u> <ul style="list-style-type: none"> • Patients had a histologic diagnosis of MPM with no prior chemotherapy treatment. • WHO performance status of 0-2. <u>Exclusion criteria:</u> <ul style="list-style-type: none"> • Unable to discontinue administration of aspirin or NSAIDs for 2 days before, the day of, and 2 days after the dose of pemetrexed. 	<u>Intervention Group 1:</u> Pemetrexed 400mg/m ² IV over 10 mins followed 30 minutes later by carboplatin area under the plasma concentration-time curve (AUC) 4mg/mL-min (as a 30 minute intravenous infusion). Repeated every 21 days. <u>Intervention Group 2:</u> Pemetrexed 500mg/m ² IV over 10 mins followed 30 minutes later by carboplatin area under the plasma concentration-time curve (AUC) 6mg/mL-min (as a 30 minute intravenous infusion). Repeated every 21 days. Other groups were included ranging from the doses used in groups 1 and 2.	A total of 163 courses of treatment were administered (median 6, range 1-10). Main toxicity was hematologic particularly neutropenia, although this was characteristically short-lived and caused few clinical problems. The maximum tolerated dose (MTD) was pemetrexed 500mg/m ² , carboplatin AUC 6. 8/25 (32%) partial responses were observed. 70% of patients noticed an improvement in symptoms, usually after 2 courses (84%). Median time to progression was 305 days, and median survival time was 451 days (15 months).	Level 3

APPENDIX 2: Characteristics of Studies Excluded from the Analysis

<i>Study</i>	<i>Reason for Exclusion</i>
Adjei, AA 2003 ²⁶	Review, not systematic
Anonymous 2003 ²⁷	Comment on some published studies.
Bischoff, HG et al 2002 ¹⁰	Review, not systematic
Boyer, MJ et al 2002 ¹¹	Review, not systematic
Budde, LS and Hanna, NH 2004 ¹²	Review, not systematic
Bunn, P et al 2001 ²⁸	Abstract only
Calvert, AH et al 1999 ²⁹	Abstract only
Catalano, A et al 2004 ¹³	Review, not systematic
Fossella, FV and Gatzemeier 2002 ¹⁴	Review, not systematic
Gadgeel, SM and HI Pass 2004 ¹⁵	Review, not systematic
Gamelin, E et al 1999 ³⁰	Abstract only
Gralla, R et al 2001 ³¹	Abstract only
Gralla, R et al 2003 ³²	Abstract only
Green, MR 2002a ¹⁶	Review, not systematic
Green, MR 2002b ¹⁷	Review, not systematic
Hanauske, A-R 2004 ¹⁸	Review, not systematic
Harrison, TS and LJ Scott 2003 ¹⁹	Review, not systematic
Johnson, T et al 1999 ³³	Abstract only
Kindler, HL 2004 ²⁰	Review, not systematic
Liepa, A et al 2002 ³⁴	Abstract only
Manegold, C 2003a ²¹	Review, not systematic
Manegold, C et al 2003b ³⁵	Abstract only
Maung, K 2002 ²²	Review, not systematic
Mayor, S 2002 ³⁶	News article
Paz-Ares, L et al 2003 ²³	Review, not systematic
Scagliotti, G et al 2001 ³⁷	Abstract only
Scagliotti, G et al 2002 ³⁸	Abstract only
Shin et al 2002 ³⁹	Abstract only
Suwanrusme, H et al 2003 ²⁴	Review, not systematic
Symanowski, JT et al 2003 ⁴⁰	Abstract only
Tomek, S and Manegold, C 2003 ²⁵	Review, not systematic
Vogelzang, NJ et al 2002a ⁴¹	Abstract only
Vogelzang, NJ et al 2002b ⁴²	Abstract only, this was later published and has been included in this review
Vogelzang, NJ et al 2003 ⁴³	Abstract only

APPENDIX 3: Search Strategy

The following databases were accessed on 6th September 2004:

Cochrane DSR

ACP Journal Club 1991 to March/April 2004

DARE 2nd Quarter 2004

CCTR 2nd Quarter 2004

EMBASE 1988-2004 week 35

OVID Medline ® 1996 to August Week 4 2004

Ovid Medline ® in process and other non indexed citations

OVID Medline daily update 1-9-04.

The search strategy utilised the following key words:

1. Pemetrexed
2. Mesothelioma
3. 1 and 2
4. Limit 3 to English
5. Limit 4 to Human

APPENDIX 4: Scottish Intercollegiate Guidelines Network (SIGN) Revised Grading System

Levels of evidence

- 1++ High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
- 1+ Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
- 1 - Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
- 2++ High quality systematic reviews of case-control or cohort studies
High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
- 2+ Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
- 2 - Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
- 3 Non-analytic studies, e.g. case reports, case series
- 4 Expert opinion

Grades of recommendation

- A** At least one meta analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or
A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
- B** A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+
- C** A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++
- D** Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+

Good practice points

- 4 Recommended best practice based on the clinical experience of the guideline development group

APPENDIX 5: Definitions of the Phases of Pharmaceutical Trials

Phase 1 Clinical Drug Trial: Phase 1 clinical drug trial represents the first test of a drug in a human population (only animal and in vitro data are available). Phase 1 trials are designed to determine toxicity, absorption, metabolism and safe dosage range and are limited to relatively few subjects (20-80). Although healthy volunteers are sometimes used, for obvious ethical reasons, Phase 1 testing is more properly done in patients. For example, cancer chemotherapy subjects in a Phase 1 trial have exhausted all alternative treatments and enrol in the study hoping for therapeutic benefit. The study often involves dose escalation until the maximum tolerated dose is established. This means the dose is increased until toxicity occurs. Obviously, subjects in a Phase 1 clinical trial of a toxic chemotherapeutic agent incur the risk of death from toxicity. Although a subject may receive therapeutic benefit from participating in a Phase 1 study, the objective in conducting the study is primarily pharmacological in nature.

Phase 2 Clinical Drug Trial: A Phase 2 clinical drug trial is a controlled clinical trial involving a limited number of subjects (200-300). It is designed to test efficacy and obtain additional data on the safety of the drug.

Phase 3 Clinical Drug Trial: A Phase 3 clinical drug trial is an expanded trial (several hundred subjects) which is designed to gain additional evidence of efficacy.

Phase 4 Clinical Drug Trial: A Phase 4 clinical drug trial is a post-marketing study of an FDA-approved drug in order to gain more information, e.g., elucidate the incidence of a specific adverse reaction or determine the long-term effects of the drug on morbidity and mortality.

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