REGIONAL DRUG AND THERAPEUTICS CENTRE
(NEWCASTLE)

THE USE OF PEMETREXED FOR THE TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA

Wolfson Unit
Claremont Place
Newcastle upon Tyne
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ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre. The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rests solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

Subject	*Date issued*
Dornase alfa	December 1994
Paclitaxel in ovarian cancer	January 1995
Interferon beta-1b in MS	February 1995 December 1995 (update)
Riluzole in ALS	October 1996
IV immunoglobulin therapy	January 1997
Abciximab in PTCA	February 1997
Recombinant FVIII	March 1997
Interferon alfa in hepatitis C	June 1997
Alglucerase for Gaucher's disease	July 1997
Taxanes in breast cancer	July 1997
Somatropin for GHD in adults	January 1998
New drugs for Alzheimer's disease	February 1998
Atypical antipsychotics	February 1998
Dornase alfa for cystic fibrosis	July 1998
Topotecan for ovarian cancer	July 1998
Irinotecan for colorectal cancer	July 1998
Interferon alfa for haematological malignancy	July 1998
Antiretroviral therapy	July 1998
Paclitaxel in ovarian cancer	December 1998 (update)
Interferon in MS	May 1999 (update)
Octreotide	July 1999
Drug treatment of obesity	July 1999
Low molecular weight heparins in venous thrombo-embolic disease	November 1999
Low molecular weight heparins in unstable coronary artery disease	November 1999
Ribavirin and interferon alfa for chronic hepatitis C	March 2000
Temozolomide for high grade gliomas	May 2000
New drugs for rheumatoid arthritis	May 2000
Verteporfin for age related macular degeneration	November 2000
Iloprost and epoprostenol in the management of pulmonary hypertension	February 2001
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Interferon alfa in the management of malignant melanoma	November 2001
Imatinib (Glivec®, STI-571), in the management of chronic myeloid leukaemia	November 2001
Agalsidase alfa and beta in the management of Fabry disease	July 2002
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SUMMARY

- **Malignant pleural mesothelioma (MPM) is a highly aggressive tumour that originates from mesothelial cells, which form the serosal lining of the pleural cavity. In Great Britain, the incidence of MPM has increased considerably in the recent years and is expected to peak at 1,950 - 2,450 deaths per year between 2011 and 2015.The aetiology of MPM is primarily linked to occupational exposure to asbestos.**
- **In the North East and Yorkshire standardised mortality ratios for MPM are significantly higher than the average for Great Britain because of the long tradition of shipbuilding, railway engineering and asbestos manufacturing.**
- **Currently, no cure exists for MPM and without treatment median survival from onset of symptoms averages 9 months. For most patients chemotherapy is the main therapeutic option, but despite many trials with numerous regimens none have consistently yielded response rates greater than 20%, and median survival remains largely unaffected.**
- **Pemetrexed is a novel multi-targeted antifolate agent that in combination with cisplatin is licensed in the EU as a treatment for chemotherapy-naïve patients with unresectable malignant pleural mesothelioma and as second-line monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer.**
- **In the largest phase III trial to date conducted in MPM, pemetrexed plus cisplatin gave a longer survival time, higher tumour response rate, longer time to disease progression, and a higher 1-year survival rate than cisplatin alone. A significant palliative effect and improvement in quality of life was also reported in the majority of patients. Anti-tumour activity in patients with MPM has also been demonstrated with pemetrexed as a single agent.**
- **The most common adverse effects when pemetrexed is used in combination with cisplatin in chemotherapy-naïve patients with MPM were neutropenia, leucopenia, fatigue, nausea and vomiting.**
- **Pemetrexed, in combination with cisplatin, is the only drug licensed for the treatment of MPM and may have potential benefits in terms of pharmacy and nursing time, ease of administration and treatment-related hospitalisations compared with other commonly used regimens.**
- **Pemetrexed should only be administered under the supervision of experienced specialists. Careful haematological and biochemical monitoring is required during treatment. Patients receiving pemetrexed must take folic acid and vitamin B_{12} supplementation to reduce treatment-related toxicity.**
- **Pemetrexed costs £800 exclusive of VAT per 500 mg vial. Based on the average patient the maximum cost per cycle would be £1,600. The median number of cycles received per patient during trials was 6, giving a total cost of £9,600.**
- **Several novel approaches to the treatment of MPM, incorporating new chemotherapeutic, biological and targeted therapies, are currently being**

investigated. A large phase III trial comparing the role of chemotherapy in the palliative treatment of MPM with best active symptom control is currently underway

BACKGROUND

Malignant pleural mesothelioma (MPM) is a highly aggressive tumour that originates from mesothelial cells forming the serosal lining of the pleural cavity. In Great Britain, the incidence of MPM has increased significantly in recent years and the total number of mesothelioma deaths is predicted to peak at 1,950 -2,450 per year sometime between 2011 and 2015.[1] The aetiology of MPM is primarily linked to occupational exposure to asbestos, a family of naturally occurring silicate materials.[2,3] However, only around 80% of patients who acquire MPM have a history of asbestos exposure.[2,3, 4] This suggests that other environmental and genetic factors may also be important in the development of this malignancy. Infection with Simian virus (SV)-40 has been implicated in the aetiology of this disease.[3, 4] Because SV-40 antigens can be found in the majority of mesothelioma patients [4] it has been postulated that asbestos and SV-40 may function as co-carcinogens.[2, 3]

Asbestos-related mesothelioma most typically develops 20-50 years after the first documented exposure, depending upon the type of fibres and intensity of exposure. Onset of disease is commonly in the fifth to seventh decade of life.[5] The disease is also found among family members of asbestos-exposed individuals, with more than half of all female patients presenting with MPM having had household contact with asbestos workers.[6] The areas with the highest mesothelioma rates for males tend to be those in the proximity of industrial sites with a history of heavy asbestos exposures. Consequently, the former North East and Yorkshire region and other areas with a long tradition of shipbuilding, railway engineering and asbestos manufacturing have standardised mortality ratios (SMRs) for MPM significantly higher than the average for Great Britain.[7] Provisional Health and Safety Executive (HSE) figures for mesothelioma mortality in the former North East and Yorkshire region (1988-2002) are summarised in Appendix 1.

Disease prognosis is difficult to assess consistently because there is great variability in the time before diagnosis and the rate of disease progression. The early symptoms of mesothelioma are often non-specific and can sometimes be confused with other illnesses such as pneumonia. Such similarities can sometimes lead to a delay in diagnosing mesothelioma. Furthermore, some patients with early stage mesothelioma may be asymptomatic. The disease usually becomes self-evident by symptoms such as pain, dyspnoea or pleural effusions.[3, 8] However, by the time such symptoms occur, the disease is often locally advanced. Currently, no cure exists for 'advanced' MPM and long-term survival for patients who develop the disease remains poor. Life expectancy for victims depends upon the stage at which the disease is detected, age and relative health of the patient as well as tumour histology. Typically, disease progression without treatment involves aggressive local growth, invasion of mediastinal structures and death within 9 months from the onset of symptoms .[3, 4, 8, 9]

Conventional therapy

Treatment options for MPM are currently limited. MPM is generally considered to be unresponsive to most therapies and treatment for all but localised mesothelioma is not curative.[3, 6, 10] The management of mesothelioma depends largely on its stage of development at diagnosis. For patients who are eligible, aggressive tri-modality

regimens that include surgery, radiotherapy and chemotherapy have shown some benefit in prolonging survival in some very highly selected subgroups of patients.[10] However, few patients are candidates for surgical resection due to the usually advanced stage of disease at first presentation.[3,6] Likewise, the tumour's large surface area and pattern of growth often limit curative radiotherapy. Surrounding the lung, its proximity to the heart, spinal column and other organs makes it difficult to deliver sufficiently high doses while avoiding toxicity to normal tissues.[10] In most cases a palliative approach aimed at symptom control and quality of life (QoL) is the only choice in the management of patients with MPM. All treatment modalities may have a role in palliation.[3, 10]

Chemotherapy remains the main therapeutic option for most patients with MPM. Numerous single-agent regimens have been evaluated for the treatment of mesothelioma; doxorubicin is the most frequently investigated chemotherapeutic agent.[6] This and other anthracycline analogues, such as epirubicin, detorubicin and pirarubicin, have in general yielded response rates of less than 20% with limited impact on median survival.[3, 6, 10] Other agents, such as cisplatin, carboplatin, mitomycin, ifosfamide, docetaxel and vinorelbine, have shown similar response rates.[6, 11] The antifolates methotrexate and edatrexate have produced more promising results, but these have not been confirmed in large-scale studies.[6, 10, 11]

Because single-agent chemotherapy regimens have failed to show clinically significant effectiveness, several combination chemotherapy regimens for MPM have been evaluated.[6, 11, 12] The majority of these have been double regimens combining anthracyclines (e.g. doxorubicin) with alkylating agents (e.g. cyclophosphamide, mitomycin or ifosfamide) or the platinum-containing agents (e.g. cisplatin or carboplatin). Triple regimens of mitomycin and vinblastine with cisplatin (MVP) or carboplatin (MVcarbo) have also been used.[6, 10, 11] Despite many trials with numerous regimens, none of the combination therapies has demonstrated a consistently greater response rate than single-agent therapy. With few exceptions, no class or combination of agents have yielded response rates consistently greater than 20%, and median survival remains largely unaffected at around 6-12 months.[3] Furthermore, such response rates do not necessarily reflect symptom relief, which is important for patients with an incurable disease.

Novel chemotherapeutic agents and their combinations appear somewhat more promising. Pemetrexed is a multi-targeted antifolate agent, which inhibits several folate-dependent enzymes, resulting in blockade of pyrimidine and purine nucleotide synthesis.[13, 14] Consequently, rapidly dividing cells, which require a continuous supply of nucleotides, stop growing or die when exposed to antifolates. Although some proliferating cells of normal tissues, such as haemopoetic and intestinal mucosal cells, are also susceptible to antifolates, such side effects can be anticipated and strategies implemented to reduce them.[14]

The purpose of this report is to review the efficacy and place in treatment of pemetrexed (Alimta® Eli Lilly and Company) as a first-line therapy in patients with MPM.

EFFICACY

Pemetrexed (Alimta®) was granted a European Licence in September 2004 and has been commercially available in the United Kingdom since November 2004. The approved indications are:[15]

- In combination with cisplatin for the treatment of chemotherapy-naïve patients with unresectable MPM.
- As monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

Limited trial data currently exists with only two trials fully published to date. The therapeutic use of pemetrexed in combination with cisplatin in chemotherapy-naïve patients with MPM has been evaluated in a single, large, phase III, randomised, single-blind, multi-centre trial.[16] A total of 448 patients were treated and considered assessable for efficacy and toxicity analyses: 226 received pemetrexed (500 mg/m^2 in combination with cisplatin (75 mg/m^2) and 222 received cisplatin (75mg/m^2) alone (intravenously on day 1 of a 21-day cycle). Dose reductions were allowed for haematological and specified non-haematological effects. Any patient requiring three dose reductions was discontinued from the study.

The primary endpoint was to compare survival times (defined as the time from randomisation to the time of death from any cause) between the two arms. Secondary endpoints included tumour response rates, time to disease progression and clinical benefit response rate.[17] A complete tumour response (CR) was defined as complete absence of measurable, non-measurable but assessable and unassessable disease, with no new lesions and no disease-related symptoms. A partial response (PR) was defined as a reduction in the sizes of target lesions of ≥30% or ≥50% in patients with uni- or bidimensionally measurable disease, respectively. Tumour progression was defined as the appearance of a new or relapsed lesion, a 25% or 50% increase in a specified assessment of uni- or bidimensionally measurable disease, respectively, deterioration of assessable disease or death from disease. Clinical benefit response was evaluated using an algorithm of performance status, analgesic consumption, patient-reported pain intensity, and dyspnoea, Lung Cancer Symptom Scale scores, pulmonary function test scores and toxicity. [16, 17]

During the study, the treatment regimen was amended (after 117 patients had enrolled) because of a high incidence of severe toxicity, including three treatment-related deaths among the first 43 patients randomly assigned to the pemetrexed arm. Folic acid and vitamin B_{12} supplementation was added to the treatment regimen in both treatment arms. This change resulted in three patient subgroups that were defined by supplemental status: never supplemented (NS) (completed treatment before the protocol change); partially supplemented (PS) (began treatment before, and completed treatment after the protocol change); and fully supplemented (FS) (began treatment after the protocol change).

After vitamin supplementation was implemented the sample size was increased to ensure adequate statistical power for analysis of the FS subgroup. The comparison of survival in the two treated arms was tested at the $\alpha = 0.0476$ level with an 80% power to detect a hazard ratio of 0.67 (a 33% reduction in the hazard ratio). The number of deaths required is 197, and n=280 (140 per arm, or subgroup) [16, 18]

The primary efficacy analysis was conducted on an intent-to-treat basis. However, the population for analysis included only randomised patients who had started treatment and therefore cannot strictly be considered an intent-to-treat analysis.[18] Even so, out of the 456 randomly assigned patients only 8 did not receive any treatment, leaving a total of 448 for the primary efficacy analysis. In view of the small number of patients actually excluded it is unlikely that re-analysis of the data based on all randomised patients would significantly alter the outcomes. [5]

Patients receiving both pemetrexed and cisplatin (ITT population) had a significantly increased median overall survival time of 12.1 months compared with 9.3 months for those receiving cisplatin alone (HR 0.77, p=0.020). The median time to progression of disease was significantly longer in those patients receiving pemetrexed plus cisplatin than cisplatin alone (5.7 versus 3.9 months, HR 0.68, p=0.001). Tumour response rates were 41.3% in the pemetrexed plus cisplatin arm and 16.7% for cisplatin alone (p<0.001). In the subgroup analysis of patients who received full vitamin supplementation (FS, n=331), the median overall survival time was 13.3 months for the pemetrexed plus cisplatin arm and 10.0 months for cisplatin alone (HR 0.75, p=0.051, borderline significance). A secondary Wilcoxon analysis (to account for early events) of the FS group did reach significance (p=0.039). Tumour response rates (numbers needed to treat (NNT) = 4) and time to disease progression were better with pemetrexed plus cisplatin than with cisplatin alone (45.5% vs. 19.6%, and 6.1 months vs. 3.9 months, respectively, both p<0.001). The one-year survival rates for the FS patients were 56.5% on the combination regimen and 41.9% on cisplatin alone (p=0.011, NNT= 7).

The median number of cycles received in the pemetrexed plus cisplatin arm was 6 cycles (range 1 to 12) versus 4 cycles (range 1 to 9) in the cisplatin arm. Patients not supplemented received a median of only 2 cycles on both arms. The relative dose intensity delivered, as a percentage of planned dose intensity was 92.4% for the pemetrexed plus cisplatin arm versus 96.4% for the cisplatin alone arm.

Quality of life (QoL) data were obtained from 448 eligible patients and measured via 100mm visual analogue scales and the validated Lung Cancer Symptom Scale for Mesothelioma (LCSS-Meso).[19] Pemetrexed plus cisplatin was significantly more effective at controlling the symptoms of MPM such as pain, dyspnoea and cough than cisplatin alone,[19] although symptom control was not deemed clinically important.[5] In addition, lung function, as measured by wider vital (slow and forced) capacity and forced expiratory volume in one second (FEV_1) improved significantly in the combined therapy group (Table 1).[17] Based on a further analysis by the United States Food and Drug Administration (FDA), this improvement in pulmonary function was deemed to be clinically significant.[5]

Single-agent pemetrexed was evaluated as a first-line treatment for MPM in one phase II trial.[20, 21] A total of 64 chemotherapy-naïve patients entered this trial and received intravenous pemetrexed (500 mg/m^2). The primary outcome determined was the tumour response rate and secondary endpoints included time-to-event parameters, QoL and lung function. After 21 patients had received treatment, the study protocol was amended as a result of preliminary clinical toxicity findings in the phase III trial. In order to improve patient safety, subsequent patients (n=43) received folic acid and vitamin B_{12} supplementation.

Of the 64 patients enrolled, none achieved a complete response, but nine (14.1%) achieved partial tumour responses (as defined in the phase III trial). Response rates

were determined in two separate analyses for the supplemented (FS) and non-supplemented (NS) subgroups. Seven of the nine responders were vitamin supplemented. The incidence of severe haematological and non-laboratory toxicity was lower in the supplemented patients. However, this trial was not prospectively designed to assess the effect of vitamin supplementation on efficacy. Median overall survival for all enrolled patients was 10.7 months (FS 13.0 months, NS 8.0 months). An improvement in symptoms, as measured by LCSS-Meso and increased lung function, was observed in those patients who achieved a clinical response.[22] However, it is difficult to interpret the results of this trial in relation to practice due to the use of pemetrexed as a single agent and the small numbers of patients involved.

Table 1. Summary of QoL data from phase III trial.

	Randomised and Treated (n=448)		
	Pemetrexed/Cisplatin (n=226)	**Cisplatin (n=222)**	**Statistics**
Patient LCSS-Meso Scores (as change from baseline LS mean for cycle 6 (positive change indicates worsening)):			
• **Fatigue**	7.05	12.74	p=0.039
• **Dyspnoea**	0.17	6.91	p=0.009
• **Pain**	-1.23	5.80	p=0.009
PFT improvement (as % predicted average change from baseline LS mean over 6 cycles):			
• **SVC**	4.80	0.15	p=0.001
• **FVC**	4.03	-0.21	p=0.002
• **FEV_1**	3.77	-1.22	p=0.001
CB response rate (hybrid)	21.2%	13.6%	p=0.073

Abbreviations: CB = clinical benefit; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; LCSS-Meso = Lung Cancer Symptom Scale for mesothelioma; LS = least squares; PFT = pulmonary function test; SVC = slow vital capacity.

ADVERSE EFFECTS

The most common treatment-emergent adverse events reported in the phase II trial were grade 3/4 neutropenia and leucopenia, which were markedly reduced by co-administration of folic acid and vitamin B_{12} (52.4% for NS vs. 9.3% for FS, and 38.1% for NS vs. 9.3% for FS, respectively), although no statistical comparison was carried out.[20]

The primary safety analysis in the phase III study was done on all patients who received at least one dose of pemetrexed and/or cisplatin (n=448).[15, 16]

Haematologic and non-laboratory adverse events were uniformly more frequent in the pemetrexed plus cisplatin recipients than cisplatin recipients. In the FS combination subgroup the most common haematologic treatment-emergent adverse events were grade 3/4 neutropenia (23.2%) and leucopenia (14.9%). The most common non-laboratory grade 3/4 adverse events in this group were fatigue (10.1%), nausea (11.9%) and vomiting (10.7%). Febrile neutropenia and neutropenic sepsis were relatively infrequent. Treatment-related skin and subcutaneous tissue disorders (rash and alopecia) were common (all grades 16.1% and 11.3 % respectively).[15]

The most common cause of dose delay in both arms was neutropenia, followed by reduced creatinine clearance, leucopenia, anaemia, stomatitis and infection. Treatment cycle 4 was associated with the most clinical delays. Three possible treatment-related deaths occurred in this phase III study before the advent of vitamin supplementation; none were reported thereafter.[16]

DOSAGE, ADMINISTRATION AND COST

To reduce the incidence of severe toxicity, patients must receive oral folic acid or a multivitamin containing folic acid (350-1,000 mcg) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive an intramuscular injection of vitamin B_{12} (1 mg) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. To reduce the incidence and severity of skin reactions, a corticosteroid, equivalent to 4 mg of oral dexamethasone twice daily, should be given the day prior to, on the day of, and the day after, pemetrexed administration.[15]

All patients eligible for pemetrexed therapy should avoid taking NSAID's with long elimination half-lives for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration. Patients with mild to moderate renal insufficiency should avoid taking for 2 days prior to, on the day of, and at least 2 days following, pemetrexed administration.[15] Careful haematologic and biochemical monitoring prior to treatment with pemetrexed is required including full blood count, differential white cell count, platelet count and renal and hepatic function tests. Details of administration, dose adjustments and the recommended monitoring parameters are given in the SPC.[15]

The recommended dose of pemetrexed is 500 mg/m^2 BSA administered as an intravenous infusion over 10 minutes on day 1 of a 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 BSA infused over 2 hours beginning approximately 30 minutes after completion of the pemetrexed infusion. Patients must receive adequate anti-emetic treatment and appropriate hydration consistent with local practice prior to and/or after receiving cisplatin.

Pemetrexed (Alimta®) costs £800 (exclusive of VAT) per 500 mg vial.[23] Based on the average patient (body surface area 1.75m^2), a standard dose would be 875 mg, giving a maximum cost per cycle of £1,600 (2 x 500 mg vials). The median number of cycles received during the phase III trial was six,[16] giving an estimated total cost of £9,600 per patient.

Using results from this trial which showed a significant increase in overall survival (3.3 months) compared with cisplatin alone in fully supplemented patients, a crude estimate of cost per life year gained (LYG) would be £34,909 (assuming the maximum dose is administered and 6 treatment cycles completed). However, the mean number of cycles completed by patients during clinical trials was four [16] (although in practice the median number of cycles used may be lower as at least half of patients may not respond). Using these figures the total cost of pemetrexed would be £6,400 and the crude cost per LYG £23,272 (exclusive of VAT).

A small audit of 30 patients with MPM treated at Wythenshawe Hospital with compassionate-use pemetrexed (alone n=2, plus cisplatin n=10, or plus carboplatin n=18) received a median of 4 cycles of treatment with a median survival of 14.7 months for those who received pemetrexed plus cisplatin (8.6 months for pemetrexed plus carboplatin).[24] These figures would give an estimated cost per LYG of £16,340 (when compared to cisplatin alone).[16] This is comparable to the costs per LYG of interventions approved by NICE for the treatment of other forms of lung cancer (£2,250 - £16,700 for combination chemotherapy and £14,000 for docetaxel as a second-line therapy).[25] However, this study is too small for reliable conclusions to be drawn. All these estimates of cost effectiveness are very crude and do not include administration or monitoring costs, the costs of treating any treatment-related adverse effects, the cost of prophylactic steroids and vitamin supplementation, nor the cost of the cisplatin, which is approximately £335 per 4 cycles of treatment, based on a body surface area of 1.75m^2 (although individual discounts may vary between hospitals).[23] They are based only on measurements of improvements in survival, which in the pivotal phase III trial are of borderline significance with wide confidence intervals (primary analysis of FS patients).[16]

A post-hoc analysis was performed on FS patients from the phase III trial that were diagnosed with advanced disease (stage III/IV) at baseline on behalf of the Scottish Medicines Consortium (SMC).[26] This subgroup analysis was chosen as it was thought to best reflect the anticipated use of pemetrexed in routine clinical practice. The economic analysis performed on this cohort for the SMC gave an incremental cost per life-year saved of £20,844 based on a survival gain of 4.8 months in those FS patients with advanced disease. [27]

PLACE IN TREATMENT

Currently in the UK, there is no generally accepted standard of treatment for patients with MPM and treatment with more than palliative intent remains inadequate. There is limited high-quality clinical evidence demonstrating that chemotherapy extends survival or improves quality of life compared with best supportive care.

The results of the largest, randomised phase III study in unresectable MPM showed that the survival difference between pemetrexed plus cisplatin and cisplatin alone in fully vitamin-supplemented patients was of borderline significance (p=0.051).[16] Furthermore, the median age of the patients studied was lower (61 years) and the performance status higher (only patients with a Karnofsky Performance Status[28] of 70 or above were eligible, Appendix 2) than those typically seen in UK practice. Thus, it is questionable as to whether comparable results could be achieved in those patients who do not meet the eligibility criteria of the trial.

However, pemetrexed in combination with cisplatin is the only drug licensed for the treatment of MPM. It has been shown to produce response rates above those observed with established treatment regimens, has acceptable toxicity (as shown by QoL data) and has a significant palliative effect in the majority of patients with MPM. Moreover, this regimen demonstrated a survival benefit of 3.3 months duration, which is clinically relevant in a disease for which previously there was no treatment option and which has a median survival from diagnosis of <1 year. Furthermore, pemetrexed plus cisplatin was associated with statistically significant quality of life benefits compared with cisplatin alone. Palliation of symptoms such as pain, dyspnoea and fatigue are a primary concern when treating patients with mesothelioma. Pain due to invasion of the intercostal nerves by the tumour can diminish the expansion of the thoracic cage and accentuate the dyspnoea which in turn reduces lung ventilation and breathing. Therefore relief of pain and dyspnoea will have a significant impact on patient's quality of life.

There is currently inadequate information available for robust estimation of cost effectiveness of pemetrexed, although preliminary data suggest that the cost per life year gained is relatively high. If this agent is to be used (pending NICE guidance) consideration should be given to limiting its use to MPM patients whose performance status and life expectancy is consistent with the entry criteria for the major phase III trial upon which the product license is based. Other patients should be enrolled onto clinical trials wherever possible.

ARRANGEMENTS FOR PRESCRIBING

Pemetrexed should only be administered under the supervision of qualified clinicians experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are available.

FUTURE DEVELOPMENTS

Several novel approaches to the treatment of MPM, incorporating new chemotherapeutic, biologic and targeted therapies are currently being investigated. These include three potential inhibitors of vascular endothelial growth factor (VEGF): bevacizumab, thalidomide and semaxinib.[29] Bevacizumab, a recombinant anti-VEGF antibody, in combination with chemotherapy (gemcitabine/cisplatin) is being investigated in a phase II trial.[12] Eli Lilly & Company currently have two ongoing trials of pemetrexed in MPM: Pemetrexed plus gemcitabine (Gemzar®) as front-line chemotherapy for patients with malignant pleural or peritoneal mesothelioma (study ID No 7214), [30] and the Phase II Trial of neo-adjuvant pemetrexed plus cisplatin followed by surgery and radiation for pleural mesothelioma (study ID No 7216).[31] The results obtained to date with the combination of pemetrexed and cisplatin in the treatment of MPM may represent the standard against which future therapies will be measured.

Crucial to the role of chemotherapy in the treatment of mesothelioma is the impact on the QoL reported by the patients. The role of chemotherapy in the palliative treatment of MPM is the subject of an ongoing randomised controlled trial sponsored

by The British Thoracic Society and Cancer Research UK (study ID No MS01).[32, 33] This large phase III trial is currently comparing best active symptom control (ASC) with or without chemotherapy. Patients are given either ASC alone, ASC plus vinorelbine or ASC with MVP (mitomycin, vinblastine and cisplatin). This trial should give a definitive answer as to whether these established chemotherapeutic agents are better than ASC alone, in terms of overall survival, symptom palliation, performance status, analgesic usage, toxicity, QoL, tumour response and progression-free survival. Pemetrexed was not included in this trial because intake to the MS01 trial started before the results of the phase III pemetrexed plus cisplatin trial were published.

NICE guidance on the use of pemetrexed in the treatment of MPM is scheduled for October 2006.

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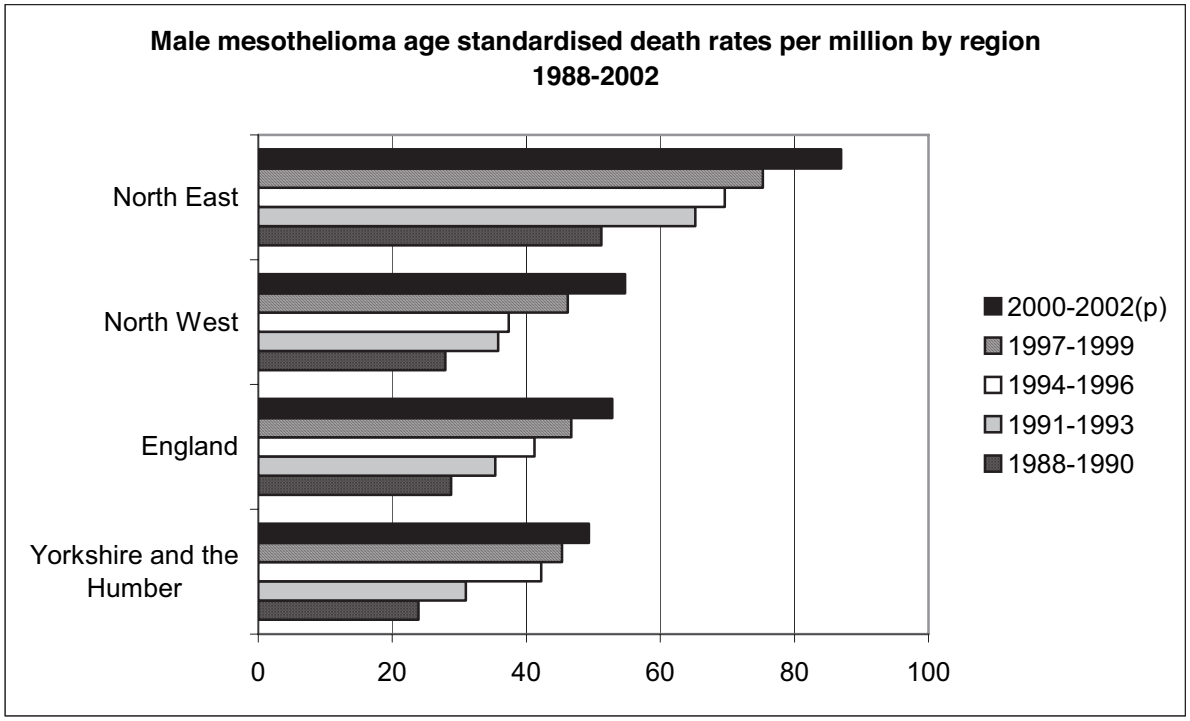
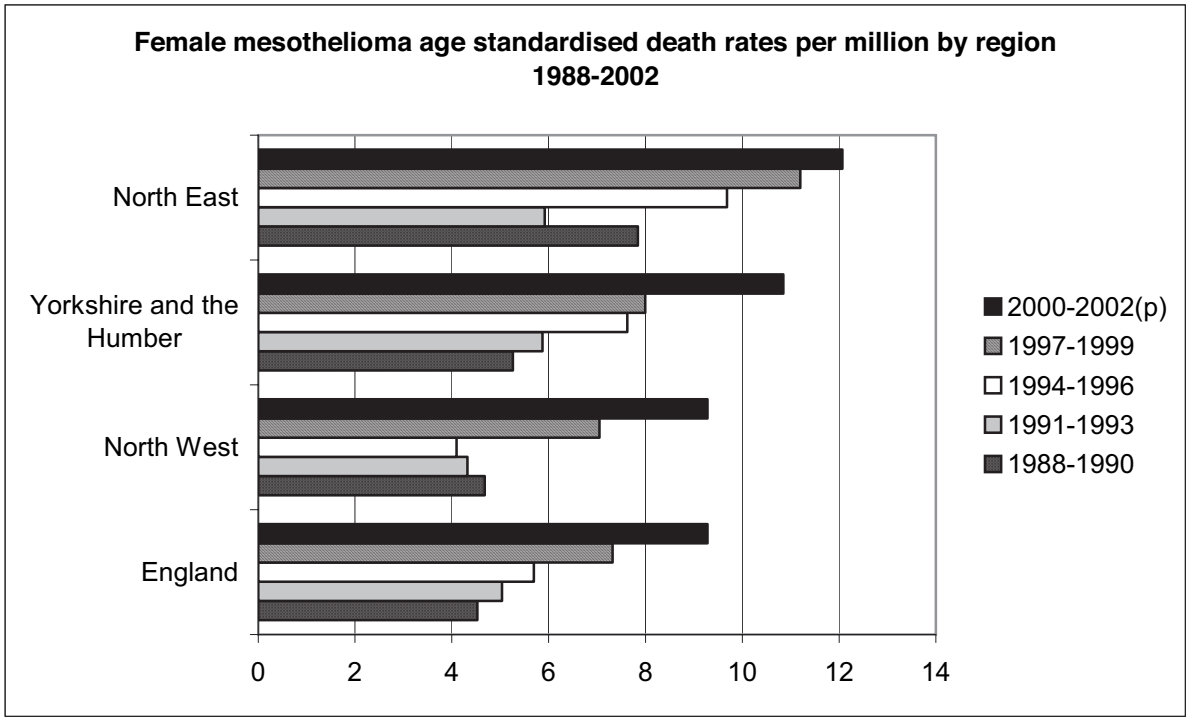
APPENDICES

APPENDIX 1. *PROVISIONAL MESOTHELIOMA MORTALITY RATES 1988-2002*





1988-90 was taken as the base for standardisation over time. (p) = Provisional data.

Adapted from HSE data.[34] A more detailed geographical breakdown can be found in the fact-sheet entitled: "Mesothelioma mortality in Great Britain: an analysis by geographical area, 1981-2000" [7]

APPENDIX 2. *KARNOFSKY PERFORMANCE STATUS SCALE*

Score	Description
100	Normal no complaints.
90	Able to carry on normal activities. Minor symptoms of disease.
80	Normal activity with effort.
70	Cares for self. Unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but able to care for most of own needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled. Requires special care and assistance.
30	Severely disabled. Hospitalisation indicated though death not imminent.
20	Very sick. Hospitalisation necessary. Active supportive treatment necessary.

Adapted from Karnofsky Performance Status Revisited: Reliability, Validity and Guidelines.[28]

APPENDIX 3. SUMMARY OF TRIALS

Key: FS - fully supplemented; i.v. - intravenous; ITT - intent-to-treat; KPS - Karnofsky performance status; MC - multi-centre; NS - never supplemented; NSAID - non-steroidal anti-inflammatory drug; O - open; Op - Outpatient; Pa - parallel arm study; PS - partially supplemented; RT – randomised and treated; SB - single-blind; Ts -two-stage.

PEMETREXED FOR MALIGNANT PLEURAL MESOTHELIOMA (MPM)

Reference	Design	Intervention	Patient numbers	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
Volgelzang et al, 2003 [16, 17, 18]	MC, R, SB, Pa	Pemetrexed 500 mg/m^2 as 10 min i.v. infusion + 30 minutes later cisplatin 75 mg/m^2 i.v. infusion over 2 h on day 1 of each 21-day cycle, maximum 6 cycles of therapy. *	RT = 226 FS = 168 PS & NS = 58	Male and female ≥18 years with uni- or bidimensionally measurable disease, life expectancy ≥12 weeks, KPS ≥70, and adequate organ function.	Prior chemotherapy, second primary malignancy, brain metastases, unable to interrupt NSAID treatment.	Overall survival time from randomisation until death from any cause.	Median survival time for ITT pemetrexed + cisplatin regimen = 12.1 months cf. 9.3 months for cisplatin alone (p= 0.020). FS pemetrexed + cisplatin = 13.3 months cf. 10.0 months for cisplatin alone (p<0.051).	Severe side effects (Grade 3/4 toxicities) were more common in the pemetrexed plus cisplatin arm than for cisplatin alone. FS patients: Neutropenia (23.2 cf. 3.1%), leucopenia (14.9 cf. 0.6%), nausea (11.9 c f. 5.5%), vomiting (10.7% cf. 4.3%), and fatigue (10.1 cf. 9.2%).
		Cisplatin alone 75 mg/m^2 i.v infusion over 2h on day 1 of each 21-day cycle, for 6 cycles of therapy. *	RT = 222 FS = 163 PS & NS = 59					
Scagliotti et al, 2003 [20, 21]	O, Ts, Op	Pemetrexed 500 mg/m^2 as 10 min i.v infusion on day 1 of each 21-day cycle. *	64 FS = 43 NS = 21	Male and female ≥18 years with uni- or bidimensionally measurable disease, life expectancy ≥12 weeks, KPS ≥70, adequate bone marrow reserve and creatinine clearance.	Prior chemotherapy, second primary malignancy, brain metastases, unable to interrupt NSAID treatment.	Objective tumour response rate.	Tumour response rate for all 64 patients enrolled was 14.1% (complete = 0 and partial = 9). FS 16.3% (complete = 0 and partial = 7). NS 9.5% (complete = 0 and partial = 2).	Neutropenia (23.4% (NS 52.4% c.f 9.3% for FS)), leucopenia (9.3% (NS 38.1% cf. 9.3% for FS)), fatigue (6.3%), febrile neutropenia (6.3%), nausea (4.7%), vomiting (3.1%) and stomatitis/ pharyngitis (3.1%)

* During the study the treatment regimen was amended, folic acid and vitamin B_{12} supplementation was added to al the treatment regimens.