TECHNOLOGY ASSESSMENT REPORT FOR THE HTA PROGRAMME
FINAL VERSION: 06 June 2005

Title:

Pemetrexed disodium for the treatment of malignant pleural mesothelioma

Details of appraisal group

Correspondence to:
Rumona Dickson, Ms
Director, LRiG
Liverpool Reviews and Implementation Group (LRiG)
Sherrington Buildings
Ashton Street
Liverpool, UK
L69 3GE
Tel: 0 151 794 5682/5067/5541
Fax: 0 151 794 5585
Email: R.Dickson@liv.ac.uk

Details of other members of the appraisal group

Bagust A   Professor, Health economics
Dodd SR   Research associate, Medical statistics
Dundar Y   Research Fellow, Clinical effectiveness
Haycox A   Senior Research Fellow, Health economics
Hill RA   Research Fellow, Clinical effectiveness
McLeod C   Training Fellow, Health economics
Walley T   Professor, Clinical pharmacology
Williamson PR   Professor, Medical statistics

A. Full title of research question

To assess the clinical and cost effectiveness of **Pemetrexed disodium** and cisplatin for the treatment of unresectable malignant pleural mesothelioma in chemo-naïve patients.

B. Clarification of research question and scope

The systematic review will examine the comparative clinical and cost-effectiveness of pemetrexed disodium (*trade name* Alimta, *synonym* multitargeted antifolate (MTA), LY231514) for the treatment of unresectable malignant mesothelioma in chemotherapy naïve patients.

Clinical comparisons
Comparisons will be made between:
- Pemetrexed disodium and cisplatin in combination versus cisplatin alone
- Pemetrexed disodium and cisplatin in combination versus supportive care (active symptom control)
- Pemetrexed disodium and cisplatin versus other commonly used alternatives (e.g. MVP (mitomycin C, vinblastin and cisplatin), or vinorelbine)

If evidence allows, clinical effects of pemetrexed disodium in subgroups of patients will be explored (such as performance status, white blood cell count, age at presentation, and presence/absence of sarcomatoid malignant mesothelioma).

Economic evaluation

The evaluation of economic evidence will include quality assessment of published cost minimisation, cost effectiveness, cost utility and cost benefit analyses. Economic models included in the industry submissions will be critiqued as appropriate.

If appropriate data are available, an economic model will be developed that extends beyond the end of data collection period of any published trial to estimate the cost effectiveness of pemetrexed disodium used in combination with cisplatin versus cisplatin alone or supportive care or other commonly used agents mentioned above. To facilitate this, access to data that allows the projection of means of additional months of survival is required. Comparisons of the likely outcomes of treatment with the likely outcomes of no treatment will be performed and patterns in the dataset will be explored to obtain a realistic range of survival benefit. From a health economics perspective, the focus is to identify where survival gain is most likely and how much it costs to achieve this. Access to IPD relating to resource use (e.g. inpatient stays associated with adverse events, cost of drug wastage) is also necessary in order to estimate true cost-effectiveness ratios.

Estimates will also be prepared of the likely budget impact that would arise for the NHS in England and Wales. These will take account of available information on current and anticipated patient numbers and service configuration for the treatment of this condition.

C. Report Methods

Search strategy

The following databases will be searched for relevant published literature for the period up to June 2005.

- CENTRAL (Cochrane Central Register of Controlled Trials)
- CDSR (Cochrane Database of Systematic Reviews)
- DARE (Database of Abstracts of Reviews of Effectiveness)
- EMBASE
- Health Technology Assessment (HTA) database
- ISI Web of Science- Proceedings (Index to Scientific & Technical Proceedings)
- MEDLINE
- NHS EED (NHS Economic Evaluation Database)
- ISI Web of Science- Science Citation Index Expanded

The search strategy used to explore MEDLINE and EMBASE is available in Appendix I. This strategy will be adopted as appropriate for the remaining databases listed above.

Research groups working on mesothelioma identified through searches of the information sources will be contacted for information about ongoing trials (e.g. National Cancer Research Network, Cochrane Cancer Network).

Bibliographies of reviews, retrieved articles and submissions to the National Institute for Clinical Excellence (NICE) will be searched for further studies.

Handsearching of recent issues of oncology journals that might not yet have been indexed in electronic databases and Internet resources will be examined for information on clinical trials and cost data. In addition, handsearching of recent oncology conference abstracts will be conducted electronically, where this facility is available (e.g. the American Society of Clinical Oncology (ASCO) annual conference).

Full details of the search strategies used and process of selection of evidence sources will be recorded.

Individual Patient Data (IPD), and in particular, the original data equivalent to that submitted to the U.S. Food and Drug Administration (FDA) for marketing approval will be sought from the drug manufacturer (Eli Lilly and Company Ltd) in order to complement any published data identified. This will prove useful if published reports do not contain adequate details of important clinical and economic events or do not include sufficient data to extract information on relative treatment effects.

Inclusion criteria

Study design	**Clinical effectiveness:** Primarily: Randomised Controlled Trials (RCTs) Secondly: In the absence of RCT data, non-RCTs (such as non-randomised Phase I trials) will be reported **Economic evaluation:** Full economic evaluations that consider both costs and consequences (cost-effectiveness, cost-utility, cost-minimisation and cost-benefit analyses)
Patient population	Chemotherapy naïve patients with unresectable malignant pleural mesothelioma
Interventions	Pemetrexed disodium* (Alimta™, LY231514, MTA) and cisplatin in combination
Comparators	• Cisplatin • Supportive care (active symptom control) • Other commonly used alternatives (e.g. vinorelbine, or MVP (mitomycin C, vinblastin and cisplatin))
Outcomes	**Clinical:** • Overall survival • Toxicity and adverse effects of treatment • Symptom palliation • Health-related quality of life • Tumour response • Progression-free survival • Patient preferences **Economic:** • Incremental cost per life year gained • Incremental cost per quality adjusted life year gained

*Note that people receiving pemetrexed disodium must also receive folic acid and vitamin B_{12}. [1]

Quality assessment strategy

All included studies will be assessed for methodological quality. The quality of clinical effectiveness studies will be assessed using criteria based on CRD Report No. 4.[2] For non-randomised controlled trials, quality assessment tools appropriate to that type of study will be used.

Cost effectiveness studies will be quality assessed using criteria updated from the checklist developed by Drummond and Jefferson.[3]

Two reviewers will independently evaluate the quality of the included studies and discuss disagreements. A third reviewer will be consulted, if necessary, to achieve consensus.

Data extraction strategy

Data from sources included in our search will be extracted as detailed below and will include information listed in Appendix II.

Data relating to study design, findings and quality will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Study details will be extracted on pre-tested data extraction forms. Time permitting, authors (and sponsors) of the studies will be contacted for missing data. Data from studies presented in multiple publications will be extracted and reported as a single study with all other relevant publications listed.

Methods of analysis/synthesis

a.   Methods of analysis for clinical studies

Individual study data and quality assessment will be summarised in structured tables and as a narrative description. Potential effects of study quality will be discussed. Results from non-RCTS will be presented narratively and if evidence allows, meta-analyses will be conducted using fixed effects models and will only include data from RCTs.

For binary outcomes, where sufficient data are available, relative treatment effects will be presented in the form of relative risks (RR) or odds ratios (OR). For continuous outcomes, mean differences will be calculated provided skewness is not too great. For time to event outcomes, log hazard ratios (log HR) will be presented. Data will be pooled only if this makes sense clinically and statistically. If estimates of log HR and its variance are not quoted directly in trial reports and IPD are unavailable, alternative aggregate data (e.g., log rank test p-value) will be extracted in order to calculate pooled HR estimates.[4, 5]

Trials that (1) provide only unplanned, interim findings (2) provide data on only sub-group of the enrolled patients, and (3) are continuing to recruit patients will be considered for inclusion in the review but will not be included in meta-analysis.

b.   Methods of analysis for economic studies

Individual study data and quality assessment will be summarised in structured tables and as a narrative description. All potential effects of study quality will be discussed.

To supplement findings from the economic literature review, additional cost and benefit information from other sources, including the industry submissions to NICE, will be collated and presented as appropriate.

Methods for estimating quality of life, costs and cost-effectiveness and/or cost/QALY

a.   Cost data

The primary perspective for the analysis of cost information will be the NHS and personal social services (PSS). Cost data will therefore focus on the marginal direct health service costs associated with drugs and interventions.

Quantities of resources used will be identified from consultation with experts, primary data from relevant sources and the reviewed literature. Unit cost data will be extracted from the literature (e.g. Personal Social Services Research Unit) or obtained from other relevant sources (drug price lists, NHS reference costs and Chartered Institute of Public Finance and Accounting cost databases). All cost data will be converted to a single year (2004) in pounds sterling.

Where appropriate, costs will be discounted at 6% per annum, the rate recommended in the current NICE guidance to manufacturers and sponsors of submissions. In the sensitivity analysis costs will be discounted by 3.5% as recommended in the current NICE guidelines.[6]

b.   Assessment of benefits

A balance sheet will be constructed to list benefits and costs arising from alternative treatment options. We anticipate that the main measures of benefit will be improved survival and quality of life.

Where appropriate, effectiveness and other measures of benefit will be discounted at 1.5%, the rate recommended in the current NICE guidance to manufacturers and sponsors of submissions. In the sensitivity analysis costs will be discounted by 3.5% as recommended in the current NICE guidelines.[6]

c.   Modelling

We will undertake a review of any industry submitted model(s). This will include a summary description of the model and a critical appraisal of key structures, assumptions, resources, data and sensitivity analysis. In addition, we will provide an assessment of the models' strengths and weaknesses and discuss the implications of using different assumptions in the model. We will explore reasons for any major discrepancies between the results obtained from assessment review model and the industry model.

Our ability to construct an economic model will depend on the data available. A formal combination of costs and benefits will also be performed, although the type of economic evaluation will only be chosen in light of the variations in outcome identified from the clinical review evidence.

If data available, the results will be presented as incremental cost per QALY ratios for each alternative considered. If sufficient data are not available to construct these measures with reasonable precision, incremental cost effectiveness analysis or cost minimisation analysis will be undertaken.

Should suitable IPD be made available and depending on the character of any IPD supplied, the nature of any variation in resource use and survival may be explored in the modelling exercise.

d.   Sensitivity Analysis

If appropriate, sensitivity analysis will be applied to our model in order to assess the robustness of the results to realistic variations in the levels of the underlying data. Where the overall results are sensitive to a particular variable, the sensitivity analysis will analyse the exact nature of the impact of variations.

Imprecision in the principal model cost-effectiveness results with respect to key parameter values will be assessed by use of techniques compatible with the modelling methodology deemed appropriate to the research question and to the potential impact on decision-making for specific comparisons (e.g. multi-way sensitivity analysis, cost-effectiveness acceptability curves etc).

The results of the evaluation will be used to estimate comparative cost-utility/effectiveness ratios under different treatment scenarios based upon appropriate subgroups of patients.

D. Handling the company submission(s)

The Liverpool Reviews and Implementation Group intends to use the industry dossier:
- as a source of data, looking for studies that meet the inclusion criteria (RCTs/other effectiveness as well as cost-effectiveness, cost utility studies and cost benefit analysis).
- to undertake an analysis of any industry models, including the strengths and weaknesses and the implications of different assumptions. The detail to which this can be undertaken will depend on the number and size of company dossiers submitted. Clarification of particular aspects of the model may be sought from the drug manufacturer.

Any 'commercial in confidence' or 'academic in confidence' data taken from the submission(s) or other sources will be <u>underlined</u> and <mark>highlighted</mark> in the assessment report.

E. Project Management

a   Timetable/milestones:

Submission	Date
Draft protocol	28 February 2005
Finalised protocol	06 June 2005
Progress report	15 August 2005
Complete, near final draft report to external reviewers and NICE Technical Lead	TBC [24 October 2005]
Final assessment report to NICE	22 November 2005

b.   Review Advisory Panel
The Group will recruit an Advisory Panel of experts to support the development of the review. Panel members may advise on specific sections of the review: clinical, healthcare policy, health economics, statistics and review methodology.

c.   External Referees
The Technology Assessment Report will be subject to external peer review by at least two clinical experts and one methodological expert. These referees will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. External expert referees will see a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. All referees are required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking. We will send external referees' signed copies to NCCHTA. Comments from the referees and our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.

d.   Competing Interests
No competing interests exist for members of the Assessment Group. Any competing interests relating to the external reviewers will be declared in the final report.

F. Appendices

I Details of MEDLINE search strategy

a. MEDLINE
1. (pemetrexed or alimta or LY231514 or MTA).af.
2. exp mesothelioma/
3. mesothelioma.tw
4. or/2-3
5. 1 and 4
6. animal/
7. human/
8. 6 not (6 and 7)
9. 5 not 8

b. EMBASE
1. (pemetrexed or alimta or LY231514 or MTA).af.
2. exp mesothelioma/
3. mesothelioma.tw
4. or/2-3
5. 1 and 4
6. limit 5 to human

II   Details of data extraction

Clinical effectiveness data to be extracted will include, but not be limited to:

Study Details
- Study bibliographic data
- Type of report (abstract, full manuscript, interim report)
- Type of study
- Methodological details of study
- Details of trial intervention
- Concomitant therapies
- Details of funding

Participants
- Age
- Sex
- Performance status
- White blood cell count
- Stage of disease
- Co-morbidity
- Number recruited or accrued

Results (data for all outcomes specified will be extracted as available)
- Overall survival
- Tumour response
- Progression-free survival
- Disease related symptom improvement rates
- Adverse events
- Drug related adverse events
- Withdrawal due to adverse events
- Time to abandoning treatment and reason
- Quality of life

Cost effectiveness data extraction will include, but not be limited to:

Study characteristics
- Type of evaluation and synthesis
- Intervention
- Study population
- Time period of study
- Country of origin

Economic model
- Type of model
- Perspective
- Model assumptions
- Biases included
- Life expectancy method

Cost data and cost data sources
- Cost items
- Cost data sources
- Discount rate
- Currency, and currency year

Outcome data and data sources
- Range of outcomes
- Outcome data sources
- Discount rate
- Main outcomes

Cost effectiveness
- Cost effectiveness ratios
- Subgroup analysis and results
- Sensitivity analysis and results
- Authors conclusions

III Details of quality assessment

a. Studies of clinical effectiveness will be assessed using the following criteria, based on CRD Report No. 4. [2]

- Was the method used to assign participants to the treatment groups really random? *(Computer generated random numbers and random number tables will be accepted as adequate, whilst inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week)*
- Was the allocation of treatment concealed? *(Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque)*
- Was the number of participants who were randomised stated?
- Were details of baseline comparability presented in terms of treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Was baseline comparability achieved for treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Were the eligibility criteria for study entry specified?
- Were any co-interventions identified that may influence the outcomes for each group?
- Were the outcome assessors blinded to the treatment allocation?
- Were the individuals who were administered the intervention blinded to the treatment allocation?
- Were the participants who received the intervention blinded to the treatment allocation?
- Was the success of the blinding procedure assessed?
- Were at least 80% of the participants originally included in the randomisation process, followed up in the final analysis?
- Were the reasons for any withdrawals stated?
- Was an intention to treat analysis included?

Items will be graded in terms of ✔ **yes** (item adequately addressed), ✘**no** (item not adequately addressed), ✔/✘*partially* (item partially addressed), **?unclear** or not enough information, **NA** not applicable or **NS** not stated.

b. Studies of cost effectiveness will be assessed using the following criteria, which is an updated version of the checklist developed by Drummond and Jefferson. [3]

Study design:
- The research question is stated
- The economic importance of the research question is stated
- The viewpoint(s) of the analysis are clearly stated and justified
- The rationale for choosing the alternative programmes or interventions compared is stated
- The alternatives being compared are clearly described
- The form of economic evaluation used is stated
- The choice of form of economic evaluation is justified in relation to the questions addressed.

Data collection:
- The source(s) of effectiveness estimates used are stated
- Details of the design and results of effectiveness study are given (if based on a single study)
- Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)
- The primary outcome measure(s) for the economic evaluation are clearly stated
- Methods to value health states and other benefits are stated
- Details of the subjects from whom valuations were obtained are given
- Productivity changes (if included) are reported separately
- The relevance of productivity changes to the study question is discussed
- Quantities of resources are reported separately from their unit costs
- Methods for the estimation of quantities and unit costs are described
- Currency and price data are recorded
- Details of currency of price adjustments for inflation or currency conversion are given
- Details of any model used are given
- The choice of model used and the key parameters on which it is based are justified.

Analysis and interpretation of results:
- Time horizon of costs and benefits is stated
- The discount rate(s) is stated
- The choice of rate(s) is justified
- An explanation is given if costs or benefits are not discounted
- Details of statistical tests and confidence intervals are given for stochastic data
- The approach to sensitivity analysis is given
- The choice of variables for sensitivity analysis is justified
- The ranges over which the variables are varied are stated
- Relevant alternatives are compared
- Incremental analysis is reported
- Major outcomes are presented in a disaggregated as well as aggregated form
- The answer to the study question is given
- Conclusions follow from the data reported
- Conclusions are accompanied by the appropriate caveats.

All items will be graded as either ✔ **yes** (item adequately addressed), ✘ no (item not adequately addressed), **?** **unclear** or not enough information, **NA** not appropriate or **NS** not stated.

IV. Background

Mesothelioma is a rare and, once onset has begun, rapidly progressive malignancy of the mesothelium, a thin membrane that lines the chest and the abdomen and surrounds the organs in these areas. The most common sites of mesothelioma are the pleura (over 90%), the lining of the lungs (pleural mesothelioma), followed by peritoneum the lining of the abdomen (peritoneal mesothelioma).

Approximately 1700 people in the UK (2004 figures) are diagnosed with malignant pleural mesothelioma each year, with around 1848 deaths annually (2001 figures).[7] Due to the high usage of asbestos in the 1970's it is estimated that the number of people diagnosed with mesothelioma each year will increase over the next 20 years to more than 3000 cases per year in Britain.[8] An estimated 65,000 cases are expected to occur between 2002 and 2050.[9]

Mesothelioma is strongly associated with asbestos exposure which can produce localised and diffuse scarring of the pleural lining of the chest cavity, and sometimes in the peritoneum. It has a long latency period varying between 20 and 50 or more years.[8]

Epidemiologic studies indicate occupational risks associated with mesothelioma. The greatest risk is linked with a variety of settings and occupations including insulation work, employment in asbestos manufacture, shipyards, and construction.[10] Because of the relationship to occupational exposure, mesothelioma is predominantly seen in males (five men to every one woman).[11]

Mesothelioma can be very difficult to diagnose, owing to the fact that there are many types of cells that that can form a mesothelioma tumour (e.g. mesothelioma cells are very similar to some types of lung cancer cells). When mesothelioma affects the pleura, the commonest symptom is persistent chest pain. This may be accompanied by other symptoms such as breathlessness, a persistent cough or hoarseness of voice. Prognosis is poor, with overall median survival ranging from 9 to 13 months.[12] The median time from first presentation to diagnosis is approximately 3 months.[13]

Surgery is only an option for a small minority of patients (1% or less) whose disease is at Stages I or II, with a 15% survival rate at 5 years.[12] However, for the majority of patients whose disease has progressed to surgically unresectable (beyond stage II), the outlook is bleak, with treatments aimed at palliation of symptoms, including pleural cavity drainage, radiotherapy, and chemotherapy.

Currently there is no gold-standard chemotherapy treatment for mesothelioma. A variety of chemotherapy regimens are used, including doxorubicin, epirubicin, mitomycin, cyclophosphamide, ifosfamide, cisplatin, carboplatin, and antifolates, with response rates ranging from 0 to 48%, although none offer a survival benefit.[14] The benefit observed with chemotherapy is usually an improvement in symptoms and/or, occasionally, some actual shrinkage in the size of the cancer

The technology

Pemetrexed disodium (*trade name* Alimta™) is an antifolate drug that exerts its antineoplastic action by disturbing folate-dependent metabolic processes essential for cell replication. Cisplatin is a platinum compound chemotherapeutic agent that has an anti-cancer activity used either as a single agent or in combination, for treatment of a wide variety of cancers (e.g. lung (particularly the small-cell type), bladder, testicular, stomach and ovarian cancers).

Pemetrexed is the first and only chemotherapy agent that has been granted a marketing approval for use in combination with cisplatin for the treatment of chemotherapy naïve patients (i.e. patients who have not previously had chemotherapy) with unresectable malignant pleural mesothelioma (MPM). Marketing approval was granted by FDA in February 2004 and by European Medicines Agency in

September 2004. In combination with cisplatin it has been shown to offer a survival benefit of approximately 3 months compared with cisplatin alone.[14]

In patients treated for MPM the recommended dose of pemetrexed is $500mg/m^2$ of body surface area (BSA) administered as an intravenous infusion over 10 minutes, followed 30 minutes later by cisplatin at a dose of $75mg/m^2$ BSA infused over two hours, on the first day of each 21-day cycle.[14] In order to reduce toxicity, patients must receive oral folic acid and intravenous vitamin B_{12} 1-3 weeks prior to the start of chemotherapy and continually throughout treatment.[1] Corticosteroids should also be administered one day prior to treatment and concomitantly for 3 days to reduce the potential for skin rashes.

The most commonly reported side effects when Pemetrexed is used in combination with Cisplatin include nausea, vomiting, fatigue, dyspnea (shortness of breath), neutropenia (reduced neutrophils), and leukopenia (reduced white blood cells).

Economics

The new combination therapy appears to offer the potential benefit of a modest survival gain, as well as an unknown variation in quality of life (positive if therapy improves patient experience, or negative if adverse events are dominant). These must be matched against the increased costs, most of which are likely to arise from the acquisition cost of drugs in the new combination therapy. Based on current BNF list prices (May 2005), the cost of 1 cycle of treatment with a combination of cisplatin and pemetrexed for MPM would be between £1400 and £1600 (or £9-10,000 for 6 cycles). This is equivalent to an annual acquisition of around £30,000 per 100,000 population in England, based on an incidence of 3.3 per 100, 000 population.[7]

V   References

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