Pharmacotherapeutic value and cost-effectiveness of pemetrexed for the treatment of mesothelioma

Review on pemetrexed in mesothelioma for ZonMw

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Date: March, 2011

SUMMARY [Dutch]

Introductie
Mesothelioom is een zelden voorkomende tumor, waarvan de meest voorkomende vorm de pleurale mesothelioom (MPM) is. De oorzaak is meestal gelegen in de blootstelling aan astbest en de ziekte heeft een latentietijd van 15 tot 50 jaar. Hoewel het gebruik van asbest niet meer is toegestaan en bij het opruimen van asbest speciale voorzorgmaatregelen moeten worden genomen, neemt de incidentie wereldwijd nog steeds toe. In 2008 bedroeg de incidentie in Nederland 500 gevallen, welke in mannen 5 keer hoger is dan in vrouwen.
In dit review wordt de literatuur over de effectiviteit, veiligheid, kwaliteit van leven en de kosten-effectiviteit van chemotherapie bij de behandeling van MPM samengevat. Hierbij wordt de behandeling ook belicht vanuit het perspectief van de patiënt, de medisch oncoloog en de apotheker.

Methode
In de databases MEDLINE, EMBASE en Cochrane is met trefwoorden gezocht naar reviews van gerandomiseerde klinische trials (RCTs) en economische evaluaties van de behandeling van MPM met pemetrexed (PEM). Tevens is met trefwoorden gezocht of na het verschijnen van de meest recente review nog nieuwe onderzoeken zijn gepubliceerd.
Een vertegenwoordiger van de patiëntenvereniging en een medisch oncoloog zijn geïnterviewd. Hierbij zijn vragen gesteld over de behandeling van MPM, de toxiciteit van de behandeling en de voorlichting bij het maken van keuzes omtrent de behandeling.

Resultaten
Er is één fase III onderzoek, de EMPHACIS trial, naar de werkzaamheid, effectivitiet, toxiciteit en kwaliteit van leven van PEM in combinatie met cisplatine (CISPEM), waarbij vergeleken is met cisplatine (CIS) alleen. Als gevolg van ernstige toxiciteit in de CISPEM arm werd het protocol gewijzigd. Om de toxiciteit te verminderen werden de patiënten gesuppleerd met foliumzuur en vitamine B12. PEM leidde tot een verbetering van de overleving met iets minder dan vier maanden. Graad 3/4 toxiciteit kwam vaker voor in de CISPEM arm. In de volledig gesuppleerde groep waren neutropenie, leukopenie, misselijkheid en braken de meest voorkomende bijwerkingen. Patiënten die met CISPEM waren behandeld hadden een significant grotere verbetering van de kwaliteit van leven.
In fase II onderzoek is de werkzaamheid van verschillende geneesmiddelen, waaronder gemcitabine en vinorelbine onderzocht. Het resultaat van deze onderzoek veronderstelt dat de werkzaamheid van deze middelen vergelijkbaar is met PEM.

Er zijn verschillende onderzoeken van de kosten-effectiviteit van CISPEM verricht op basis van de gegevens van de EMPHACIS trial. In het algemeen werd geconcludeerd dat het voordeel van de behandeling beperkt wordt door de bijwerkingen. Verder was de kosten-effectiviteit acceptabel. Wel was de kosten-effectiviteit beter voor patiënten met een goede conditie.

Conclusie

Geconcludeerd kan worden dat de werkzaamheid, veiligheid en kwaliteit van leven van de behandeling met CISPEM bij MPM voldoende is onderbouwd. Verder kan geconcludeerd worden dat er voldoende gegevens over de kosten-effectiviteit van PEM voor handen zijn.

INTRODUCTION

Type of disease

Mesothelioma is a rare and rapidly increasing malignancy of the mesothelium. There are three principal types of mesothelioma. The most common form is pleural mesothelioma (MPM) derived in the lining of the lung known as the pleura. The other types of mesothelioma are pericardial mesothelioma, affecting tissues over the heart, and peritoneal mesothelioma, affecting the gastrointestinal tract. Mesothelioma is caused by the exposure to asbestos. The average latency period between first exposure to asbestos and diagnosis is 15 to 50 years. This means that most cases are in a critical case by the time symptoms appear and mesothelioma is diagnosed. The 5-year survival rate in the Netherlands is 5% (1).

Epidemiology

Epidemiological studies indicate that incidence rates of mesothelioma are increasing worldwide. In 2008 more than 500 new cases with mesothelioma are diagnosed in the Netherlands, giving an age standardised incidence rate (ESR) of 2.6 per 100,000 population. Comparing cancer networks within the Netherlands, the incidence rates varied between 1.8 and 3.9 per 100,000 population. The age standardised incidence and mortality rates of mesothelioma in the Netherlands remained stable over the past 20 years. Mesothelioma affects mainly older men who in their youth were exposed to asbestos in the workplace. The incidence is six times higher in Dutch men compared to Dutch women, in 2008 more than 430 men were diagnosed with mesothelioma (ESR 4.5) vs. 70 women (ESR 0.6) (1).

Licensed chemotherapy for MPM

Treatment options for MPM are surgery, radiation therapy and/or chemotherapy. Chemotherapy is recommended either alone for medically inoperable MPM patients or as part of a regimen for patients with medically operable MPM. The current standard of care for the first-line treatment includes a combination therapy with pemetrexed and cisplatin (CISPEM).

The present review includes pemetrexed (PEM) which is registered on the ‘Beleidsregel dure geneesmiddelen in ziekenhuizen’ as expensive medicine. PEM has been licensed in the Netherlands since 2004 for the treatment of chemotherapeutic-naïve patients with MPM. PEM is also indicated for the treatment of non-small cell lung cancer. PEM is a cytotoxic medicine which belongs to the group anti-metabolites. The molecular structure of PEM was developed by a US university in New Jersey (2). PEM is converted into an active form that blocks the activity of the enzymes that are involved in producing nucleotides. The formation of DNA and RNA slows down and prevents the cells from dividing. PEM is manufactured and

marketed by Eli Lilly and Company (3). No generic versions of PEM are available. The recommended dose for first-line treatment for MPM includes 500 mg/m2 of PEM, administered in a 10-minute infusion on day 1, followed by 75 mg/m2 of CIS, administered in a 2-hour infusion 30 minutes after the administration of PEM, every 3 weeks.

Objective

A systematic review of the recent literature on treatment with an ‘expensive’ medicine in malignant pleural mesothelioma (MPM) was performed. The objectives for the review were to evaluate the pharmacotherapeutic value and cost-effectiveness of pemetrexed (PEM) for the treatment of MPM and to evaluate the impact on quality of life.

METHODS

Search strategy

A search was performed by an experienced librarian using the MEDLINE, EMBASE and Cochrane databases. The search strategies, based on terms on MPM, PEM and either randomised clinical trial (RCT) or economic evaluations, are presented in Appendix A. The search included both Medical Subject Headings (MeSH) terms, e.g. “Mesothelioma”, as well as text words. The search strategy was adapted accordingly for the EMBASE and Cochrane databases.

Selection criteria

Selection criteria that were used to include studies:

- Systematic reviews (and RCTs and economic evaluations if published after inclusion date for studies in the review)
- Patients with MPM
- Treatment with PEM

Criteria for considering studies for inclusion

Systematic reviews that investigated the pharmacotherapeutic value and cost-effectiveness of PEM for the treatment of MPM were included. Additional phase III RCTs and economic evaluations published after the publication date of the most recently performed reviews were included. Inclusion criteria for economic evaluations were cost-effectiveness analysis, cost-utility analysis and cost-minimisation analysis.

Type of studies included

Participants

Studies that included patients with MPM were included.

Type of intervention

First-line treatment (defined as the first chemotherapy regimen administered) of MPM with PEM used in combination with other chemotherapeutic therapy were eligible for inclusion.

Data collection and analysis

Two reviewers (JH and CB) independently evaluated all titles and abstracts. To streamline the data collection process, all references were exported and managed using Reference Manager, Version 11 (Thomson ISI ResearchSoft, Berkeley, CA, USA). Full paper manuscripts of potentially relevant titles/abstracts were obtained and assessed for inclusion.

Studies that did not fulfil all criteria were excluded. Disagreements were resolved by discussion until consensus was reached.

Outcomes

Data on the following outcome measures were eligible for inclusion in this review:

- Efficacy, effectiveness, toxicity, and quality of life is based on a systematic search of the literature on RCTs.
- Ongoing clinical trials on MPM were searched on the Clinical Trials Registry of the U.S. National Library of Medicine (www.clinicaltrials.org, accessed February 2011) and the Dutch Trial Registry (www.trialregister.nl, accessed February 2011).
- Clinical guidelines are reviewed including VIKC-Landelijke richtlijn (Dutch), National Institute for Health and Clinical Excellence (NICE) guidelines (UK), European Respiratory Society (ERS) guidelines (Europe), and National Comprehensive Cancer Network (NCCN) guidelines (US).
- Daily clinical practice includes an interview with one dedicated oncologist, dispension data of a hospital pharmacy of a academic medical centre in the Netherlands, and input of the patients' association.
- Data on generic products are retrieved from the Dutch Medicines Evaluation Board (CBG).
- Data on costs are retrieved from the Dutch Foundation for Pharmaceutical Statistics (SFK).
- Economic evaluation is based on a systematic search of the literature including cost-effectiveness analysis and cost-utility analysis.

RESULTS

REVIEW OF PHARMACOTHERAPEUTIC VALUE

In total 74 publications were identified. Of these 74 publications, two systematic reviews (4;5) and two reviews (6;7) on the effectiveness of PEM in the treatment of MPM were identified. The results are summarized in Table 1.

CISPEM vs. CIS monotherapy

The four reviews included described the only phase III trial, the EMPHASIS trial, comparing CISPEM and CIS monotherapy in 448 patients who were not eligible for curative surgery (8). In the CISPEM group, PEM was given intravenously over 10 minutes at a dose of 500 mg/m2, followed by CIS at a dose of 75 mg/m2 over two hours. Both drugs were administered on day 1 of each 21 day cycle. Severe toxicity in the PEM arm (e.g. drug-related death, neutropenia, febrile neutropenia, and diarrhoea) led to a change in the trial protocol. As a result, all subsequent patients in both treatment arms (to maintain blinding) received dietary folic acid (350 to 1000 µg, daily 1-3 weeks before and during study) and vitamin B12 supplementation (1000 µg IM injection, before treatment and repeated every 9 weeks). This resulted in three patient subgroups. In the intention-to-treat population, the median survival time was significantly longer ($p = 0.02$) for patients treated with CISPEM (13.2 months) then for those treated with CIS monotherapy (9.3 months). In the fully supplemented subgroup of patients (n=331), median survival was 13.3 months in the CISPEM group, compared with 10 months in the CSI-monotherapy group, which was of borderline significance ($p = 0.051$). This difference remained significant when both fully supplemented and partially supplemented (n=47) subgroups were included (13.2 months in the combination group vs. 9.4 months in the CIS group; $p = 0.022$). In the never supplemented subgroup (before the protocol change; n=70)) there were no statistically significant differences between the two groups. In the intention-to-treat population, the median time to progressive disease was 5.7 months in the combination arm of CISPEM compared with 3.9 months in the CIS monotherapy arm ($p = 0.001$). A similar difference was observed in both fully supplemented patients and combined fully supplemented/partially supplemented subgroups. In addition, a significantly longer time to treatment was obtained for patients treated with CISPEM than for those treated with CIS monotherapy. The partial RR (decrease of at least 50% of the tumour mass) was 41.3% in the CISPEM group and 16.7% in the CIS monotherapy group (Fisher's exact $p<0.001$).

Belli et al. (6) reviewed the effectiveness of single agent and combination chemotherapy. A variety of single agent and combination regimens were evaluated in clinical trials and the RR were around 0 - 45%. CIS was the most effective single agent, with carboplatin (CARBO) having similar activity and less toxicity. Vinorelbine is one of the agents that induces the highest RR in monotherapy (24%) and is associated with a median overall survival (OS) of 10.6 months. Gemcitabine as a single agent leads to RR between 0 and 31%. In the past, the anthracyclines were considered the mainstay of the MPM treatment, but doxorubicin had a modest activity (complete response and partial response of 11%). Combination therapy was generally more effective than single agent treatment (OS = 10 vs. 8.1 months). In particular, platinum-based chemotherapy had a greater RR than non-platinum combinations (24 vs. 8%) and the combination of doxorubicin and CIS showed the highest RR. With CIS and vinorelbine median OS was 16.9 months, progression-free survival (PFS) 7.2 months with a response rate (RR) of 29.6%. The combination of CIS and gemcitabine led to a RR between 12 and 48% and median OS times of 9.4 – 13 months. The efficacy of CARBO and gemcitabine has also been reported with a 1-year survival rate of 53% and progression time of 40 weeks. A phase II study (9) investigated PEM and gemcitabine and reported a RR between 17 and 26% and median survival of 8.1-10.1 months. Jackman et al. (2009) (7) presents similar figures. In addition, they discussed the results of a retrospective of case within British Columbia, showing no difference in median survival between patients treated with CISPEM and those treated with CIS plus gemcitabine.

Table 1 : Study on first-line treatment in MPM

Study	n	Drug	Median survival (months)	TTPD (months)	PRR (%)
EMPHASIS	226	CIS + PEM	13.2	5.7	41.3
Vogelzang et al. 2003	222	CIS	9.3	3.9	16.7

Abbreviations: CIS=cisplatin; PEM=pemetrexed; TTPD=time to progressive disease; PRR=partial response rate.

TOXICITY

The EMPHASIS trial comparing CISPEM versus CIS monotherapy in 448 patients found in the intention-to-treat population an incidence of grade 3/4 adverse events which was significantly more frequent in patients receiving CISPEM than in those receiving CIS monotherapy. The most commonly reported grade 3/4 adverse events
in the combination arm included neutropenia (27.9%), leukopenia (17.7%), nausea (14.6%) and vomiting (13.3%). Supplementation of folic acid and vitamin B12 led to a consistent reduction in the severity and incidence of toxicity (except for dehydration) in the CISPEM

arm. The most common grade 3/4 adverse events in the fully supplemented patients were neutropenia (23.2%), leukopenia (14.9%), nausea (11.9%) and vomiting (10.7%).

QUALITY OF LIFE

The assessment of quality of life in the EMPHASIS trial has been published only in a conference abstract form (10). Using the Lung Cancer Symptom Scale-meso instrument, several aspects of quality of life, including pain, dyspnoea, fatigue, anorexia and cough were evaluated. Patients treated with CISPEM demonstrated significantly greater improvement in global quality of life ($p = 0.0012$) when compared to those treated with CIS monotherapy. This was the case in both the intention to treat population and fully supplemented populations.

ONGOING PHASE III TRIALS

One phase III trial on treatment of MPM is currently conducted (Table 2).

Table 2 : Ongoing phase III randomised clinical trials on treatment of MPM

Trial nr.	Study start	Participants	Intervention	Outcome
NCT00651456 MAPS	2008 Recruiting	n=445	CIS + PEM + bevacizumab vs. CIS + PEM	1 RR 2 OS

Abbreviations: CIS=cisplatin; PEM=pemetrexed; OS=overall survival; RR=response rate.

REVIEW OF GUIDELINES

In the Netherlands, one guideline has been published that is relevant for PEM in MPM:

- VIKC guidelines, Mesothelioom, Regionale richtlijn IKL, versie 1.1, 2005 (11)

Other international guidelines include:

- NICE guidelines, Pemetrexed for the treatment of malignant pleural mesothelioma, 2010 (12)
- NCCN guidelines, Malignant Pleural Mesothelioma. V.1.2010 (13)
- Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma, 2010 (14)

The most important aspects of these guidelines in relation to PEM are summarised below.

The Dutch guideline recognizes the value of treatment with CISPEM combination chemotherapy. The NICE guideline recommends treatment with PEM for patients with advanced disease, who are not eligible for surgical resection. World Health Organization (WHO) performance status of the patient should be 0 or 1.
The NCCN guideline recommends chemotherapy with CISPEM for patients with stage II-III MPM. Other first-line treatment options recommended are PEM with CARBO and CIS with gemcitabine.
The ESR, in collaboration with the European Society of Thoracic Surgeons (ESTS), recommend platinum and PEM or raltitrexed as first-line combination chemotherapy for patients in a good performance status. Alternatively, patients could be included in first- and second-line clinical trials. In the light of limited evidence of efficacy of chemotherapy, the decision to administer chemotherapy should be discussed with the patients and their relatives on a case-by-case basis, like all other treatment modalities without curative purposes. Patients demonstrating prolonged symptomatic and objective response with first-line chemotherapy may be treated again with the same regimen in the event of recurrence. In other cases, inclusion of the patients in clinical trials is encouraged.

DAILY CLINICAL PRACTICE

Structured interview

One medical oncologist from a oncology medical centre in Amsterdam, the Netherlands, was invited to participate in a structured interview. The items discussed were the number of patients with MPM, treatment regimens used for MPM, treatment and prevention of toxicity, participation in studies, and means of informing and counselling patients. The total number of new patients with stage IB-IV MPM in this hospital is approximately 100, an estimated 40 patients are treated in and 60 patients come for a second-opinion.

Almost all patients receive chemotherapy treatment. Some patients have an advanced age including co-morbidity or poor performance status, that chemotherapy is not advised. All patients receive 4 cycles CISPEM as first-line treatment. For patients relapsing after first-line treatment and requiring second-line treatment, PEM and vinorelbine are considered. The interviewed medical oncologist preferred a randomized Phase I clinical trial as second-line treatment.

Hospital admission because of PEM associated toxicity is rare according to all oncologists. CISPEM combination therapy is less well tolerated in patients with MPM compared with patients with lung cancer. Most important toxicity with CISPEM treatment is fatigue. When treatment includes CIS, Emend® is used to prevent toxicity, i.e. nausea. Also, vitamins are generally prescribed.

The interviewed medical oncologist reported that no guidelines are currently used for the treatment of MPM. The best guidelines at the moment come from the ESR and has recently been published in the European Respiratory Journal (14). Dutch guidelines are being developed based on the European recommendations from the ESR. It would be worthwile to study the use of this guideline in daily practice.

Participation, inclusion and treatment in trials for the second-line treatment of MPM is preferred. Two Phase III trials, 1) comparing vorinostat vs. placebo, and 2) studying the antiangiogenic agent thalidomide after first line chemotherapy, have recently closed inclusion. The first study included 70 patients in the last year. The second study included 230 patients of whom 80% treated in the oncology centre of the interviewed oncologist. The fact that the first study randomised with placebo highlights the importance of trials for the second-line treatment of MPM. One RCTs is currently performed at the oncology centre of the interviewed oncologist. Patients are randomised in either chemotherapy or chemotherapy with angiogenic agent.

Input of patients' association

A representative of the patients' association for patients who have been exposed to asbestos, mainly mesothelioma patients, was invited to participate in a structured interview. The main function of this patients' association is to support patients in the decision-making process including the appeal for second-opinion. According to the representative of the patients' association, most patients are satisfied with the information and decision-making process. Patients are informed in consult about the possible options for treatment and the effectiveness and toxicity of treatment. A possible improvement mentioned by the representative and what they are working on is that patients are better informed, in an early stage, because of the low survival rate.

In the past, the patients' association had an important role in the availability of new medicines. The representative of the patients' association mention the availability of PEM for the treatment of chemotherapeutic-naïve patients with MPM. In 2003, PEM was only studied in the United States and not available for administration in the Netherlands. Since 2005, PEM

has been registered in the Netherlands. In cooperation with the Dutch Cancer Society, the patients' association has had a major role realizing the authorization of PEM in the Netherlands. The representative mentioned a possible reason for this struggle that the OS of PEM was only small compared to less expensive treatment.
Generally the representative of the patients' association believes that patients are not aware of the costs of the treatment offered. In addition, no concerns about the availability of treatment are experienced by patients.

Illustration of pharmacy dispension data
It was not possible to provide an illustration based on dispension data of the hospital pharmacy of one academic medical centre. In 2009-2010, only one patient with MPM was treated at the department of internal medicine. According to the pharmacy dispension data, this patient has not received parenteral chemotherapy for the treatment of MPM.

COSTS

Since 1990, the Dutch Foundation for Pharmaceutical Statistics (SFK) has been collecting and analyzing exhaustive data about the use of pharmaceuticals in the Netherlands. The expenditure increase can primarily be traced back to the increasing use of 'expensive' medicines. Along with the increasing use of expensive medicines, the expenditures grew because of a substantial nationwide growth in the number of prescriptions (15). In 2008 in the Netherlands, the total costs of expensive medicines for the treatment of cancer were € 94.3 million, slightly higher than in 2007 when the total costs were € 90.4 million. PEM has been registered as 'expensive' medicine since 2005. The total costs of PEM increased from € 1.9 million in 2005 to € 9.8 million in 2008. PEM is marketed as Alimta by Eli Lilly and Company and has been registered in the Netherlands in 2004 for the treatment of chemotherapeutic-naïve patients with MPM. No generic versions of PEM are available (3). The costs per 500mg vial of PEM decreased from € 1733 in 2008 to € 1584 in 2010 (16). These numbers represent the overall costs of PEM including all indications. No data are available to estimate what part of the total costs is contributed to the treatment of MPM.

REVIEW OF ECONOMIC EVALUATIONS

In total 16 publications were identified. Of these 16 publications, two reports were identified including all studies until 2007 on the cost-effectiveness of PEM (4;12). One additional study

was identified examining the cost-effectiveness of PEM with data from the EMPHACIS trial (17). All figures were recalculated to Euros and corrected for 4% inflation per year from the year of publication till 2011. The results of the economic evaluation are summarized in Table 3.

CISPEM vs. CIS monotherapy vs. standard care

The NICE published guidelines in the treatment of MPM based on a systematic review and economic evaluation (4;12). The review identified one economic evaluation, available only as a conference presentation/abstract by Davey et al. (18). This conference abstract included an incremental cost-effectiveness analysis of CISPEM vs. CIS monotherapy for the treatment of MPM in Australia. Data were derived from the EMPHACIS trial (8). The period of observation was 27 months. The additional mean cost of CISPEM, over CIS monotherapy, was € 13,046 per patient. The cost per life-year saved was € 68,309 for mean and € 55,996 for median incremental survival. Davey et al. suggested that a combination therapy of CISPEM offers an acceptable ICER for a small population of MPM patients in Australia. Because this is an abstract only, it was not possible to assess the validity of this study.
Two economic models were submitted by the manufacturer, Eli Lilly and Company Limited, in order to analyze the cost-effectiveness of 1) CISPEM vs. CIS monotherapy and 2) CISPEM vs. mitomycin C, vinblastine and CIS combination (MVP), vinorelbine (with or without platina) and best supportive care. Data came from the EMPHACIS trial with an observation period of 29 months. The first model was based on individual patient data, considering four subgroups: fully supplemented, fully supplemented with advanced disease, fully supplemented with good performance status, and fully supplemented with advanced disease and good performance status. The second model included data on costs and outcomes from the fully supplemented population in the first model.

The results of the review by Dundar et al. (4) suggested that PEM is unlikely to be considered cost-effective at conventionally accepted thresholds in the UK for all patients. This is mainly due to the high costs of PEM itself compared with CIS. The findings were better for fully supplemented patients with good performance status and advanced disease. The ICER per quality-adjusted life-year (QALY) saved were estimated at € 69,459 for the fully supplemented patients, € 64,897 for the fully supplemented with advanced disease population, € 67,896 for the fully supplemented patients with good performance status, and € 50,036 for the fully supplemented patients with good performance status and advanced disease population. Given the relatively small number of patients with MPM, the overall budget impact of PEM would be unlikely to be more than € 6.8 million per year at present costs.

Cordoni et al. (17) examined the cost-effectiveness with data from the EMPHACIS RCT (n = 448) evaluating two analyses designed to model best survival outcome over time for a number of patient cohorts. A first model compared the cost-effectiveness of CISPEM therapy versus CIS monotherapy (Model 1) based on patient-level trial data. A second analysis (Model 2) compared the mean costs and outcomes associated with CISPEM therapy with MVP, vinorelbine and active symptom control, using trial-based data and data extrapolated from a review of the literature. The total cost per patient for treatment with CISPEM varied between € 11,508 and € 11,825 for all cohorts studied in Model 1. The average survival gain over 29 months was between 0.20 and 0.28 life-years. Quality-adjusted life-years ranged from 0.13 to 0.31. Based on both mean and median results, Model 1 showed that the ICER per life-year gained ranged from € 26,842 to € 58,028 and the ICER per quality-adjusted life-year ranged from € 38,076 to € 89,928. The second cost-effectiveness analysis (Model 2) showed ICERs ranging from € 19,133 to € 42,037.
The authors concluded that the cost-effectiveness of CISPEM therapy seems acceptable when compared with CIS monotherapy and alternative treatments commonly used in UK clinical practice.

Table 3 : Results of economic evaluations on PEM for the treatment of MPM

Study	Type of economic evaluation	Perspective used	Time frame	Unit cost data	Source of effectiveness data	Source of resource use data	Intervention	OS (months)	Total costs	Cost-effectiveness (ICER)
Davey et al. 2005	Cost-effectiveness analysis	Australian healthcare system	27 months	Direct medical costs	EMPHASIS	EMPHASIS	CIS + PEM CIS	12.1 9.3	NA NA	€ 68,309 / LYS
Dundar et al. 2007	Cost-effectiveness review	UK	29 months	Direct medical costs	EMPHASIS	EMPHASIS	CIS + PEM CIS	NA NA	NA NA	€ 50,036 to € 69,459 / QALY
Cordoni et al. 2008	Cost-effectiveness analysis	UK	29 months	Direct medical costs	EMPHASIS	EMPHASIS	CIS + PEM CIS	NA NA	€ 11,508-11,825	€ 38,076 to € 89,928 / QALY
							CIS + PEM MVP, vinorelbine or BSC	NA NA	NA NA	€ 19,133 to € 42,037 / QALY

Abbreviations: CIS=cisplatin; PEM=pemetrexed; MVP= mitomycin C/vinblastine/cisplatin; BSC=best supportive care; OS=overall survival; ICER=incremental cost-effectiveness ratio; LYS=life year saved; QALY=quality-adjusted life year.

DISCUSSION AND CONCLUSION

One phase III trial, the EMPHACIS trial, on the efficay, effectiveness, safety and quality of life of CISPEM compared with CIS monotherapy has been performed. Severe toxicity in the CISPEM arm (e.g. drug-related death, neutropenia, febrile neutropenia, and diarrhoea) led to a change in the trial protocol. In order to reduce toxicity, patients were supplemented with dietary folic acid and vitamin B12. PEM resulted in a less than four months increase of OS in both never supplemented and supplemented patients. Grade 3/4 toxicity of CISPEM was more common in patients treated with CISPEM as compared to CIS monotherapy. The most common grade 3/4 adverse events in the fully supplemented patients were neutropenia, leucopenia, nausea and vomiting. Patients treated with CISPEM demonstrated significantly greater improvement in global quality of life when compared with those treated with CIS monotherapy.

In phase II studies the effectiveness of other drugs including gemcitabine, vinorelbine have also been performed. The results of these studies suggest similar activity of these drugs.

Several studies of the cost-effectiveness of PEM using data from the EMPHACIS trial, have been performed. The benefit of the treatment was limited as the result of substial toxicity. It was concluded that cost-effectiveness was generally well accepted, but cost-effectiveness was better for patients with a good performance status.

It can be concluded that the effectiveness, safety and quality of life of treatment with CISPEM is sufficiently supported by data from a randomised controlled trial. In addition, sufficient data on the cost-effectiveness of the treatment are available.

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ACKNOWLEDGEMENTS

We thank H. Westgeest, resident oncologist and E. Boven, medical oncologist of the VU University Medical Center Amsterdam, for cooperation in the preparation of the manuscripts. We thank R. Otten, clinical librarian of VU University Amsterdam, for his assistance in the literature search. We thank M. den Brok, hospital pharmacist of the VU University Medical Center Amsterdam, for providing pharmacy dispension data. We also thank the medical oncologists and the representative of the BC patients' association, for participating in the structured interview.

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APPENDIX A

Search strategy.

PUBMED Search History (25-11-2010)

Search	Most Recent Queries	Time	Result
#13	Search #8 AND #12	03:07:14	7
#12	Search "Costs and Cost Analysis"[Mesh] OR economic*[tw] OR Cost[tiab] OR Costa*[tiab] OR Costb*[tiab] OR Costc*[tiab] OR Costd*[tiab] OR Coste*[tiab] OR Costf*[tiab] OR Costg*[tiab] OR Costh*[tiab] OR Costi*[tiab] OR Costj*[tiab] OR Costk*[tiab] OR Costl*[tiab] OR Costm*[tiab] OR Costn*[tiab] OR Costo*[tiab] OR Costp*[tiab] OR Costq*[tiab] OR Costr*[tiab] OR Costs*[tiab] OR Costt*[tiab] OR Costu*[tiab] OR Costv*[tiab] OR Costw*[tiab] OR Costx*[tiab] OR Costy*[tiab] OR Costz*[tiab]	03:06:42	594338
#11	Search #8 AND #9 Limits: Publication Date from 2009	03:05:32	60
#10	Search #8 AND #9	03:05:04	244
#9	Search randomized controlled trial [pt] OR controlled clinical trial [pt] OR clinical trial [pt] OR comparative study [pt] OR evaluation studies [pt] OR "randomized controlled trials as topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "double-blind method"[MeSH Terms] OR "single-blind method"[MeSH Terms] OR "clinical trials as topic"[MeSH Terms] OR "placebos"[MeSH Terms] OR "research design"[MeSH Terms:noexp] OR "follow-up studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "cross-over studies"[MeSH Terms] OR "drug therapy"[Subheading] OR "clinical trial" [tw] OR "latin square" [tw] OR placebo* [tw] OR random* [tw] OR control[tw] OR controll*[tw] OR prospectiv* [tw] OR volunteer* [tw] OR trial[tiab] OR groups[tiab] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw]))	03:04:53	6208173
#8	Search #6 AND #7	03:04:15	288
#7	Search pemetrexed[tw]	03:04:03	1000
#6	Search #2 OR #3 OR #4	03:02:32	13242
#4	Search (mesothelial[tiab] OR submesothelial[tiab]) AND (cancer*[tiab] OR carcinoma*[tiab] OR neoplas*[tiab] OR tumour*[tiab] OR Tumor[tiab] OR tumora*[tiab] OR tumorb*[tiab] OR tumorc*[tiab] OR tumord*[tiab] OR tumore*[tiab] OR tumorf*[tiab] OR tumorg*[tiab] OR tumorh*[tiab] OR tumori*[tiab] OR tumorj*[tiab] OR tumork*[tiab] OR tumorl*[tiab] OR tumorm*[tiab] OR tumorn*[tiab] OR tumoro*[tiab] OR tumorp*[tiab] OR tumorq*[tiab] OR tumorr*[tiab] OR tumors*[tiab] OR tumort*[tiab] OR tumoru*[tiab] OR tumorv*[tiab] OR tumorw*[tiab] OR tumorx*[tiab] OR tumory*[tiab] OR tumorz*[tiab])	03:02:02	2043
#3	Search mesothelioma*[tiab] OR celothelioma*[tiab]	03:01:08	9933
#2	Search "Mesothelioma"[Mesh]	03:00:30	9846

EMBASE Search History (8-12-2010)

No.	Query	Results	Date
#12	#6 AND #11	11	8 Dec 2010
#11	'cost benefit analysis'/exp OR 'cost effectiveness analysis'/exp OR 'cost utility analysis'/exp	119618	8 Dec 2010
#8	#6 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [2009-2011]/py	18	8 Dec 2010
#7	#6 AND ([cochrane review]/lim OR [controlled clinical trial]/lim	79	8 Dec 2010

No.	Query	Results	Date
	OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)		
#6	#4 AND #5	676	8 Dec 2010
#5	'pemetrexed'/exp OR pemetrexed:mn,tn,ab,ti	3225	8 Dec 2010
#4	#1 OR #2 OR #3	15512	8 Dec 2010
#3	mesothelial:ab,ti OR submesothelial:ab,ti AND (cancer*:ab,ti OR tumor*:ab,ti OR tumour*:ab,ti OR carcinoma*:ab,ti OR neoplas*:ab,ti)	2288	8 Dec 2010
#2	mesothelioma*:ab,ti OR celothelioma*:ab,ti	11501	8 Dec 2010
#1	'mesothelioma'/exp	8577	8 Dec 2010

Cochrane Search History (25-11-2010)

ID	Search	Hits	Edit	Delete
#1	(mesothelioma* OR celothelioma*):ti,ab,kw	137	edit	delete
#2	(mesothelial OR submesothelial):ti,ab,kw and (cancer* OR tumor* OR tumour* OR carcinoma* OR neoplas*):ti,ab,kw	16	edit	delete
#3	(#1 OR #2)	153	edit	delete
#4	(pemetrexed):ti,ab,kw	106	edit	delete
#5	(#3 AND #4)	25	edit	delete
#6	(#5), from 2009 to 2010	1	edit	delete