Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation

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Executive summary

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Executive summary

Objectives

The review aimed to assess the clinical effectiveness and cost-effectiveness of pemetrexed disodium in combination with cisplatin for the treatment of unresectable pleural mesothelioma in chemotherapy-naïve patients.

Background

Mesothelioma is a rare and rapidly progressive malignancy of the mesothelium. About 90% of cases involve the pleura (lining of the lungs) and the remainder affect the peritoneum (lining of the abdomen). Epidemiological studies indicate that incidence is increasing worldwide, and this increase is being attributed to previous exposure to asbestos.

Currently there is no gold-standard treatment for mesothelioma. Surgical treatment is an option for only a small minority of patients whose disease is at Stage I or II. Other treatment options may include chemotherapy, radiotherapy or supportive care.

Benefits of chemotherapy may include an improvement in symptoms and/or, occasionally, shrinkage in the size of the cancer. Various chemotherapy regimens (either as single agent or in combination) are used, including mitomycin, vinorelbine, platinum compounds, doxorubicin and antifolates.

Pemetrexed disodium, a new multitargeted antifolate, is the first and only chemotherapy agent that has been granted marketing approval for use in combination with cisplatin (administered with vitamin B_{12} and folic acid) for the treatment of chemotherapy-naïve patients with unresectable malignant pleural mesothelioma.

Methods

The review was conducted following accepted guidelines for conducting systematic reviews including the identification of clinical and economic studies (1980 to May 2005), application of inclusion criteria, quality assessment of included studies and data extraction and analysis.

Inclusion criteria

Studies that compared pemetrexed disodium plus cisplatin with other cytotoxic agents or supportive care were considered for inclusion in the review. Data on the following outcome measures were considered: overall survival, toxicity, health-related quality of life, tumour response and progression-free survival.

Full economic evaluations that compared two or more options and considered both costs and consequences including cost-effectiveness, cost–utility analysis or cost–benefit analysis undertaken in the context of high-quality randomised controlled trials (RCTs) were considered for inclusion in the review.

An assessment was also carried out of the economic submission received from the manufacturer of pemetrexed comprising two sections, each employing a separate economic model. One of these models was then reformulated in order to carry out a separate exploration of economic performance.

Results

Clinical findings

One RCT comparing pemetrexed and cisplatin with cisplatin alone, and involving a total study population of 448 patients, met the inclusion criteria. The search failed to identify any other studies that compared the effectiveness of pemetrexed disodium and cisplatin with other commonly used alternatives such as vinorelbine, MVP (mitomycin C, vinblastine and cisplatin) or supportive care.

Pemetrexed in combination with cisplatin in this trial showed a 2.8-month gain in median survival compared with cisplatin alone in an intention-to-treat (ITT) population (12.1 and 9.3 months, respectively, $p = 0.020$, hazard ratio of 0.77). During the trial, increased reporting of severe toxicity in the pemetrexed arm led to a change in the protocol to add vitamin B_{12} and folic acid ▶

supplementation to therapy. For fully supplemented patients (n = 331) the hazard ratio for median survival in favour of pemetrexed plus cisplatin was also comparable (0.75), but of borderline significance between treatment arms (p = 0.051).

The trial inclusion criteria restricted recruitment to those with a Karnofsky performance status of 70 or greater (equivalent to ECOG/WHO 0 or 1 scales more widely used in the UK). Quality of life scores using the Lung Cancer Symptom Scale demonstrated significantly greater improvement for pain and dyspnoea for patients in the combination group compared with those in the cisplatin group.

In the ITT population, the incidence of serious toxicities with pemetrexed plus cisplatin was higher compared with cisplatin alone. However, the grade 3/4 toxicities of the combination arm, particularly leucopenia, neutropenia and diarrhoea, were found to be greatly improved by the addition of vitamin B_{12} and folic acid.

Economic evaluation

The existing published economic literature is very limited. Only one economic evaluation, available as a conference presentation, was identified for inclusion in the review.

The economic evaluation that we conducted (and that submitted by the manufacturer) suggests that pemetrexed is unlikely to be considered cost-effective at conventionally accepted thresholds in the UK for all patients. This is mainly due to the high cost of pemetrexed itself compared with cisplatin. These findings were better for some patient subgroups, e.g. especially for fully supplemented (FS) patients with good performance status (0/1) and advanced disease (AD). These findings seem robust.

Our estimated cost-effectiveness results were as follows:

- FS population: incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) gained = £59,600
- FS with AD population: ICER per QALY = £47,600
- FS with performance status 0/1 population: ICER per QALY = £49,800
- FS with performance status 0/1 and AD population: ICER per QALY = £36,700.

Implications for the NHS

Given the relatively small (albeit increasing) numbers of patients with mesothelioma, the overall budget impact to the NHS is likely to be in the range of £3–6 million. This assumes that only 25% of the malignant pleural mesothelioma (MPM) population are eligible for pemetrexed therapy. Most of this cost is the acquisition cost of pemetrexed itself. Whether pemetrexed plus cisplatin is to be recommended to the NHS requires careful consideration, given the extent by which the ICER exceeds conventional thresholds and the size of the NHS budget impact.

Conclusions

Mesothelioma will be a growing challenge for the NHS over the next 15–20 years, as patient numbers increase. Its poor prognosis is in part the result of late diagnosis but mainly due to the natural history of the tumour. This prognosis and the clinical course in which pain is often a prominent feature command our attention. That it is a condition brought on by occupational exposure may increase our sense of needing to respond to these patients.

Any new treatment promising palliation or increased life expectancy therefore may seem very attractive. In evaluating a new treatment, however, we need to consider what current best care is for such patients. Many patients receive only supportive care, in part related to the late stage of presentation. The concept of best supportive care is somewhat nebulous: it is almost synonymous with active symptom control and ideally it would consist of adequate pain relief managed by an experienced palliative care team who would also offer other forms of support to both patients and their families. However, this low-technology and low-cost approach is in practice not available to all patients. It would be sad if any new therapy attracted attention and resources away from this fundamental approach, which should be available to all patients.

The new therapy examined in this document demonstrates an extension of life expectancy and palliation, as measured by time to progression of disease and other end-points. The comparator in this trial was cisplatin, itself an unproven therapy in mesothelioma but justified on the grounds that there are no established regimens of chemotherapy proven to be of benefit in mesothelioma. This is strictly correct and the evidence presented is compelling, in several analyses, including those of the US Food and Drug Administration looking at fully supplemented patients at various stages of ▶

disease. This is the largest trial yet conducted in mesothelioma, an impressive achievement, and will remain the best available evidence for some time to come. However, the absolute benefit obtained is small, and it needs to be weighed against the benefits of effective palliative care services. The limited benefit was also at the expense of considerable toxicity to patients. While the severe toxicities in early use were ameliorated by vitamin B_{12} and folic acid supplementation, even thereafter the incidence of toxicity was high.

The information on quality of life, which might be expected to capture the patient's perception of the balance between benefit and toxicity and of effective palliative care, is limited at present and, for the economic evaluation presented here, it has been necessary to assume that data from other forms of lung cancer apply in this condition also.

Interestingly, the extension of life (2.8 months) was less than that previously suggested to be acceptable to patents with non-small cell lung cancer when weighed against the toxicity of a cisplatin-based chemotherapy regimen. Although the dose of cisplatin is important in determining toxicity, the extent to which patients would weigh the pemetrexed plus cisplatin regimen with its greater toxicity than cisplatin alone against a limited extension of life is unknown. It would seem that this is an issue of providing enough information about the risks and benefits of this therapy to allow them to make their choice.

The comparator in this study, cisplatin as monotherapy, is not the form of chemotherapy most widely used in the UK for mesothelioma. A large multicentre Phase III randomised trial of the most widely used treatments, mitomycin, vinblastine and cisplatin against vinorelbine and compared with active symptom control, is under way. Given that this trial also addresses the important question of whether any chemotherapy is better than supportive care, it would be unfortunate if this trial could not be carried on as a consequence of the pemetrexed plus cisplatin trial or a National Institute for Health and Clinical Excellence appraisal.

We believe that any decision to use pemetrexed plus cisplatin in an individual patient needs to be in full collaboration with that patient, against a background of high-quality palliative care services. The patient needs to be well informed of the benefits and toxicities of the regimen. Much more research is needed into the optimum chemotherapy for these patients and a clear definition of what constitutes best supportive care.

The economic evaluation conducted here and that of the manufacturer suggest that pemetrexed is not cost-effective at conventional thresholds for all patients. These findings seem robust. Cost-effectiveness seems better for some patient subgroups, e.g. especially for patients with good performance status and with advanced disease, where it is estimated the ICER per QALY would be £36,700. Given the relatively small number of patients with mesothelioma, albeit increasing, the overall budget impact of pemetrexed would be unlikely to be more than £5 million per year at present costs.

Recommendations for further research

Other agents including anthracyclines and antimetabolites require further evaluation in mesothelioma, in combination with pemetrexed. The use of sequential and also combination chemotherapy should be considered.

The role of supportive care needs to be defined and evaluated. In order to generalise the treatment findings, further studies including patients with poor performance status are needed. Such trials also need to include an assessment of appropriate quality of life data to inform subsequent economic evaluations better.

Publication

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