predictor of outcome in COPD.[12] The answer to the important question of whether the prognosis can be altered by increasing functional performance is not known. The arguments are somewhat analogous to those about the presence of nutritional depletion in severe COPD, where a low body mass index is associated with increased mortality but attempts to change the situation by supplementation have been ineffective.[13 14] In the case of physical function, however, it is clear that the simple intervention of exercise training will improve performance and have a prolonged effect on lifestyle.[15] It would therefore be reasonable to test the hypothesis that rehabilitation can reduce hospital readmission in an appropriately susceptible group.

In the UK a hospital admission for COPD generally involves a length of stay of 8 days.[9] From the patient's perspective, there is a flurry of attention at the beginning of the admission followed by 7 days of observed inactivity. As result, patients may leave hospital less well equipped for independent life than when they were admitted. Characteristically, our hospital and community services are attuned to dealing with one crisis but make little attempt to prevent the next. The huge financial costs of hospital admissions for exacerbations of COPD deserve some exploration of the value of actions that may prevent the initial admission or reduce the frequency of readmission. The cost of drug treatment for these patients is second only to the cost of hospitalisation, but to adhere to the 20th century view that drug treatment alone will provide all the answers is a delusion. The diverse factors associated with advanced COPD require a multimodality approach by a multiprofessional team. There is now increasing evidence that non-pharmacological interventions may play a major role. Let us hope that this evidence is now persuasive enough to promote appropriate investment in research and services for this neglected condition.

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Pleural mesothelioma

# The new front line treatment for malignant pleural mesothelioma?

**J P C Steele**

The presentation at the recent meeting of the American Society of Clinical Oncology of the results of the largest phase III trial in malignant pleural mesothelioma has aroused renewed interest in the treatment of this cancer. What are the implications for the ongoing UK mesothelioma trial?

Malignant pleural mesothelioma has become a mainstream cancer. This is partly due to the increasing incidence,[1 2] but is also a result of the advances being made in its treatment. This summer the American Society of Clinical Oncology Annual Meeting plenary session included a clinical research paper on malignant pleural mesothelioma for the first time.[3] In fact, this may well have been the first oral presentation on the disease at this important international meeting. The reason for the increased interest is that the study presented is the largest phase III randomised trial reported in malignant pleural mesothelioma. The trial, which recruited internationally and was led by researchers at the University of Chicago, showed a positive clinical benefit for an experimental arm based on a novel chemotherapy drug. But what do these data mean for respiratory physicians, oncologists and patients, and is this a definitive result? What effect, if any, does this trial result have on the ongoing UK mesothelioma trial?

The University of Chicago multicentre trial compared a combination of pemetrexed and cisplatin chemotherapy with a control arm of single agent cisplatin. Pemetrexed is a new cytotoxic drug that inhibits several folate dependent reactions that are essential for cell proliferation, hence its previous name "multitargeted antifolate".[4] Its primary target is thymidylate synthase, but it also inhibits folate dependent enzymes involved in purine synthesis. It is related to the existing cytotoxic drugs methotrexate, 5-fluorouracil, and raltitrexed. Phase I and II data had suggested a dose for a 21 day cycle of 500–600 mg/m$^2$ pemetrexed and 75–100 mg/m$^2$ cisplatin, with both drugs being administered on the same day.[5 6] The investigators of the phase III trial chose doses of 75 mg/m$^2$ cisplatin and 500 mg/m$^2$ pemetrexed for the experimental arm. Patients randomised to the control arm received 75 mg/m$^2$ cisplatin. All patients were treated every 3 weeks.

A total of 472 patients with malignant pleural mesothelioma were recruited between 1998 and 2002. All had good performance status (Karnofsky score 70–100%). After an initial accrual period, four drug related deaths from febrile neutropenia were noted (three in the experimental arm and one in the control arm). These deaths were linked to raised homocysteine levels and it was decided to give all patients folic acid supplements and vitamin B12 to counter this. This measure appeared to reduce the toxicity of the chemotherapy in both arms of the study. The researchers reported that, for the complete cohort of patients, the combination therapy significantly lengthened the time to disease progression (5.7 months *v* 3.9 months; p=0.001) and overall survival (12.1 months *v* 9.3 months; p=0.020). For patients receiving full vitamin supplementation, the overall survival for those treated with pemetrexed and cisplatin was 13.3 months compared with 10.0 months for the control patients (p=0.051). The study organisers concluded that the combination of pemetrexed and cisplatin with folic acid and vitamin B12 should now be considered the "standard front line therapy for patients with malignant pleural mesothelioma".

In the UK the British Thoracic Society has recently completed the pilot phase of a randomised trial of chemotherapy for patients with malignant pleural mesothelioma.[7] The trial—known as "MESO-1"—started as a feasibility study because the investigators wanted to determine which of two quality of life instruments was more appropriate. MESO-1 contained a multiple randomisation option such that patients and their oncologists could choose to be randomised between active symptom control (ASC) versus one of two chemotherapy regimens or between the chemotherapy regimens only. The chemotherapy regimens chosen were single agent vinorelbine for 12 weeks and MVP (mitomycin C, vinblastine and cisplatin) for four 21 day cycles. These regimens were chosen because they both give a response rate of approximately 20% and have proven quality of life benefit in a substantial proportion of patients.[8 9]

Following completion of the pilot study, the trial has been granted full support from Cancer Research UK and the National Cancer Research Network and is now designated "MSO1". This three arm phase III trial aims to randomise 840 patients with malignant pleural mesothelioma into one of three arms: ASC without chemotherapy; ASC with vinorelbine chemotherapy; and ASC with MVP chemotherapy. The main end points of MSO1 are overall survival, symptom palliation, quality of life, toxicity, response, and recurrence. One hundred and fifty patients from the pilot study who were randomised between all three arms will be included in the MSO1 analysis.

The important question is whether the MSO1 trial is still ethical in the light of the new data on pemetrexed with cisplatin. I think the answer is "yes". The University of Chicago trial, although promising and an important step in the advancement of knowledge of mesothelioma, can be criticised. Firstly, what was the rationale for the control arm? Few physicians would recommend single agent cisplatin in a dose of 75 mg/m$^2$ to a patient with mesothelioma: the response rate is likely to be low[10] and toxicity—especially in patients with constitutional symptoms—can be appreciable. Choosing a control arm of limited efficacy may have made the pemetrexed and cisplatin combination appear more effective than it was. Indeed, from the quality of life data currently available, the symptom scores of patients treated with cisplatin 75 mg/m$^2$ appeared to worsen on treatment, thus exaggerating the palliative benefit of the experimental treatment and emphasising why trials including a "no chemotherapy" arm may be appropriate.

Secondly, the investigators concluded that pemetrexed with cisplatin, folic acid and vitamin B12 should be the "standard front line therapy" for patients with malignant pleural mesothelioma. However, the data for patients given this exact combination showed that the improvement in overall survival compared with the questionable control arm only achieved borderline statistical significance (p=0.051).

These criticisms weaken the argument that pemetrexed with cisplatin and vitamin supplementation should be standard treatment, although the combination is certainly an option for fitter patients. A randomised trial including a "no chemotherapy" arm remains reasonable, and the pilot phase of the UK trial has shown that patients are willing to be randomised into such a trial. The MSO1 trial, with its comprehensive set of end points, should define the role of palliative chemotherapy in malignant pleural mesothelioma. It demands our full support, as do other trials examining new treatments for this once neglected group of cancer patients.

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