Clinical and cost effectiveness of paclitaxel, docetaxel, gemcitabine, and vinorelbine in non-small cell lung cancer: a systematic review

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Background: Lung cancer remains a devastating disease with few effective treatment options. Recent developments in chemotherapy have led to cautious optimism. This paper reviews the evidence on the clinical and cost effectiveness of four of the new generation drugs for patients with lung cancer.

Methods: A systematic review of randomised controlled trials (RCTs) identified from 11 electronic databases (including Medline, Cochrane library and Embase), reference lists and contact with experts and industry was performed to assess clinical effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine. Clinical effectiveness was assessed using the outcomes of patient survival, quality of life, and adverse effects. Cost effectiveness was assessed by development of a costing model and presented as incremental cost per life year saved (LYS) compared with best supportive care (BSC).

Results: Of the 33 RCTs included, five were judged to be of good quality, 10 of adequate quality, and 18 of poor quality. Gemcitabine, paclitaxel, and vinorelbine as first line treatment and docetaxel as second line treatment appear to be more beneficial for non-small cell lung cancer than BSC and older chemotherapy agents, increasing patient survival by 2–4 months against BSC and some comparator regimes. These gains in survival do not appear to be at the expense of quality of life. Survival gains were delivered at reasonable levels of incremental cost effectiveness for vinorelbine, vinorelbine with cisplatin, gemcitabine, gemcitabine with cisplatin, and paclitaxel with cisplatin regimens compared with BSC.

Conclusion: Although the clinical benefits of the new drugs appear relatively small, their benefit to patients with lung cancer appears to be worthwhile and cost effective.

Despite reductions over recent decades, lung cancer remains the leading cause of death from cancer and the third most common cause of all deaths in England and Wales with around 29,000 deaths per annum. The outlook for patients following diagnosis is poor; 80% die within 1 year with only 5% surviving 5 years. Survival rates vary within England and Wales and across Europe.

About 10% of patients with lung cancer are diagnosed early enough for cure by surgery, but most receive palliative care with radiotherapy and/or chemotherapy. Chemotherapy has often been considered toxic and ineffective, but recent developments have led to cautious optimism as a result of improvements in symptom relief, quality of life, and survival. It has been hoped that the new generation drugs such as paclitaxel, docetaxel, gemcitabine, and vinorelbine will provide sufficient benefit to dispel the nihilism surrounding lung cancer in the UK. Funding of chemotherapy varies among health authorities in England and Wales, partly due to uncertainties about their benefit but also because of concerns about the costs of the drugs and the possibility of realising any potential savings.

In view of the continuing uncertainty over the clinical and cost effectiveness of the new chemotherapy agents and the “postcode prescribing” that has resulted, the National Institute for Clinical Excellence (NICE) was asked to provide national guidance for England and Wales. This paper summarises the results of a systematic review and economic evaluation commissioned to assist NICE in their deliberations on the clinical and cost effectiveness of paclitaxel, docetaxel, gemcitabine, and vinorelbine for patients with lung cancer.

Methods

Systematic review of clinical effectiveness

We searched for published studies in the English language using 11 electronic databases including Medline, Cochrane library, Embase, and Cancer Trials from their inception to December 2000 (search strategy reported elsewhere). Additional references including unpublished studies were sought by searching bibliographies of related publications and by contact with experts and industry. Studies reported only as abstracts or conference presentations were excluded.

Randomised controlled trials (RCTs) of paclitaxel, docetaxel, gemcitabine, and vinorelbine separately or in combination in the treatment of patients with lung cancer were included. Studies had to include either best supportive care (BSC), other new regimens, older regimens, or platinum-based combination regimens. The term BSC is used to describe care which includes relief of symptoms by, for example, analgesics, but which does not attempt to prolong life or to remove (even if only temporarily) the cause of the symptoms. BSC may vary in its inclusions. For example, radiotherapy may be part of palliative care by providing temporary relief of metastatic symptoms. Studies of chemotherapy as an addition to surgery or radiotherapy were excluded. Outcome measures included patient survival, quality of life, and adverse events. Tumour response was excluded from the review because of the poor correlation with symptom relief and patient survival.

The quality of the RCTs was assessed using the Jadad scale. This required cautious interpretation given the difficulties associated with blinding RCTs in chemotherapy, particularly when compared with BSC where the maximum score will be 3 rather than 5. Inclusion criteria were applied, data were extracted, and quality was assessed by one reviewer and checked by a second reviewer, with any differences being resolved by consensus.

Clinical effectiveness was assessed using a narrative comparison of different outcomes including median survival,
1 and 2 year survival, and differences in quality of life parameters. Meta-analysis was precluded by the diversity of interventions and comparators, differences in or insufficient details on outcomes used, patient characteristics, and drug dose and administration.

**Economic evaluation: the lung cancer costing model**
Given the preclusion of a meta-analysis and to make the analysis more robust, three modelling approaches were adopted: pairwise comparisons between the regimens (or BSC) from actual published trials; a cost minimisation analysis (CMA); and a cost effectiveness analysis (versus BSC) through synthesis of efficacy data by patient numbers. The pairwise and cost minimisation results are presented elsewhere. These were attempted for completeness but methodological concerns and the small size of the trials confounded the pairwise data while the usefulness of a CMA in policy decision making is limited.

**Sources of costs and resource utilisation**
Sixteen economic evaluations were found but none were UK based. A lack of readily available cost data hampered construction of a UK cost effectiveness model. Collection of costs was restricted to available published and unpublished data including detailed “bottom up” costing work done by the Scottish Health Purchasing Information Centre (SHIPIC), the Scottish Health Service Cost’s “blue book”, and information from Southampton General Hospital. Unit costs are published elsewhere. Drug regimen costs were taken from the British National Formulary (BNF) using common trial dosages and based on a body surface area (BSA) of 1.7 m². The cost of antiemetics and diuretics used in the trials was negligible and was excluded from the analysis. More modern drugs such as ondansetron are much more expensive but may also be more effective. Questions remain about the appropriate number of administrations per cycle and whether one cycle of one regimen is equivalent to one cycle of another. These points are also discussed elsewhere in detail.

Best supportive care costs were based on data from case notes of 36 patients with stage IV non-small cell lung cancer (NSCLC) receiving terminal care, with adjustments for costs of inpatient care, outpatient care, home visits by primary care teams, and treatment costs relevant to BSC. This was the only known UK calculation of BSC. However, these data were cross checked against raw data from a larger series from the South-East Scotland Lung Study (SESLS). BSC estimates from SESLS were found to be similar to our previous figures. In the absence of available specific cost data on adverse events, a figure of £500 based on expert advice was added to account for such things as admission for drug induced neutropenia. This was applied irrespective of regimen, although it may vary between the four drugs with the cost for the taxanes perhaps being higher.

**Source of efficacy data**
Efficacy was analysed in terms of median survival since the response is not necessarily indicative of increased length of life. For the model, median survival by regimen was based on data from case notes of 36 patients with stage IV non-small cell lung cancer (NSCLC) receiving terminal care, with adjustments for costs of inpatient care, outpatient care, home visits by primary care teams, and treatment costs relevant to BSC. This was the only known UK calculation of BSC. However, these data were cross checked against raw data from a larger series from the South-East Scotland Lung Study (SESLS). BSC estimates from SESLS were found to be similar to our previous figures. In the absence of available specific cost data on adverse events, a figure of £500 based on expert advice was added to account for such things as admission for drug induced neutropenia. This was applied irrespective of regimen, although it may vary between the four drugs with the cost for the taxanes perhaps being higher.

**RESULTS**

**Quantity and quality of clinical effectiveness studies**
Searching did not find any studies assessing the clinical effectiveness of the four drugs for treating small cell lung cancer. We included 33 RCTs to assess clinical effectiveness of the four drugs for treatment of NSCLC; three assessed docetaxel,1314151617 six gemcitabine,13 1618202124–26 and docetaxel and five combined treatments.12 13 14 16 17 18 19 20 21 24–26

**Clinical effectiveness of docetaxel**
Of the three RCTs (table 1), two compared docetaxel with BSC as either first14 15 or second line treatment,19 while the other compared docetaxel with vinorelbine or ifosfamide as second line treatment.17 Docetaxel appeared to increase median survival compared with BSC (table 2), although the benefit was only shown to be statistically significant when docetaxel 75 mg/m² was used as second line treatment, improving median survival by nearly 3 months (docetaxel 75 mg/m² versus BSC 4.6 months, p=0.01).17 One year survival rates were significantly higher for patients given docetaxel 75 mg/m² (32%, 95% CI 23 to 40; p<0.05) compared with vinorelbine or ifosfamide (19%, 95% CI 12 to 26) as second line treatment.17 The effect of docetaxel on quality of life was assessed as first and second line therapy compared with BSC (table 3).14 15 As first line treatment, docetaxel had a limited effect on global health status and physical functioning but significantly improved emotional functioning (p<0.05), nausea/vomiting (p<0.05), pain (p<0.0001), and dyspnoea (p<0.05).15 When used as second line treatment, docetaxel had a significant beneficial effect on pain (p<0.01).17 Adverse effects varied between the different interventions. Haematological toxic events were more frequent among those receiving docetaxel than either BSC or vinorelbine or ifosfamide. In contrast, reporting of non-haematological toxic events differed little between docetaxel, BSC, and vinorelbine or ifosfamide. Higher toxic death rates were reported for patients...
Table 1: Characteristics of studies of clinical effectiveness

<table>
<thead>
<tr>
<th>Study details</th>
<th>Design</th>
<th>Intervention</th>
<th>Subjects</th>
<th>Conflicts of interest</th>
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<tbody>
<tr>
<td>Docetaxel</td>
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<tr>
<td>Shepherd et al</td>
<td>2/3</td>
<td>Phase II, multicentre, randomised trial. ITT</td>
<td>Second line treatment: DOC 100 mg/m² (49 patients), DOC 75 mg/m² (55 patients), and BSC (100 patients)</td>
<td>Stage IIIA/B or IV NSCLC, None stated</td>
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<tr>
<td>Roszkowski et al</td>
<td>2/3</td>
<td>Phase III, open-label, multicentre, randomised trial. ITT</td>
<td>First line treatment: DOC 100 mg/m² (137 patients) every 3 weeks, BSC (70 patients)</td>
<td>Stage IIIb or IV NSCLC, Supported by Rhone-Poulenc Rorer</td>
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<tr>
<td>Fossella et al</td>
<td>2/5</td>
<td>Phase III, open-label, multicentre, randomised trial. ITT</td>
<td>Second line treatment: DOC 100 mg/m² (125 patients), DOC 75 mg/m² (125 patients), VNB or IFO5 (123 patients)</td>
<td>NSCLC stage IIIb/IV, Supported by Rhone-Poulenc Rorer</td>
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<td>Gemcitabine</td>
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<td>Anderson et al</td>
<td>3/3</td>
<td>Multicentre, randomised trial. ITT</td>
<td>GEM 1000 mg/m² with BSC (150 patients); BSC (150 patients)</td>
<td>Symptomatic locally advanced or metastatic NSCLC, Supported by Eli Lilly and Company</td>
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<tr>
<td>Bakkel Huink et al</td>
<td>2/5</td>
<td>Phase II, multicentre, open-label, randomised study. Not ITT</td>
<td>GEM 1000 mg/m² (72 patients); CDDP 100 mg/m² with VP-16 100 mg/m² (75 patients)</td>
<td>Stage IIIa (inoperable), IIIb or IV NSCLC, Supported by Eli Lilly and Company</td>
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<td>Cardenal et al</td>
<td>2/5</td>
<td>Phase III, multicentre, randomised trial. ITT</td>
<td>GEM 1250 mg/m² (69 patients); VP-16 100 mg/m² (66 patients)</td>
<td>Stage IIIb or IV NSCLC, Supported by Eli Lilly and Company</td>
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<td>Crino et al</td>
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<td>Pong et al</td>
<td>2/5</td>
<td>Phase II, randomised trial. ITT</td>
<td>GEM 1000 mg/m² with CDDP 100 mg/m² (153 patients); MTO 6 mg/m², IFOS 3000 mg/m², with CDDP 100 mg/m² (TriComb) (152 patients)</td>
<td>Stage III (A or B) or IV NSCLC, None stated</td>
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<td>Sanders et al</td>
<td>1/5</td>
<td>Phase III, multicentre, randomised trial. ITT</td>
<td>GEM 1000 mg/m² with CDDP 100 mg/m² (260 patients); CDDP 100 mg/m² (262 patients)</td>
<td>Stage IIIa or IIIb or IV NSCLC, Supported by Eli Lilly</td>
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<td>Paclitaxel</td>
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<td>Bonomi et al</td>
<td>2/5</td>
<td>Phase III, multicentre, randomised trial. Not ITT</td>
<td>VP-16 100 mg/m² with CDDP 75 mg/m² (193 patients); PAC 125 mg/m² with CDDP 75 mg/m² (190 patients)</td>
<td>Stage IIIb or IV NSCLC, None stated</td>
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<td>Chang et al</td>
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<td>Ranson et al</td>
<td>2/3</td>
<td>Phase III, multicentre, randomised trial. ITT</td>
<td>PAX 250 mg/m² (25 patients); MER 1000 mg/m² (35 patients); PIR 150 mg/m² (44 patients)</td>
<td>Stage IV NSCLC, None stated</td>
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<td>Postmus et al</td>
<td>2/5</td>
<td>Phase II, multicentre, randomised trial. ITT</td>
<td>PAX 250 mg/m² (25 patients); MER 1000 mg/m² (35 patients); PIR 150 mg/m² (44 patients)</td>
<td>Stage IV NSCLC, None stated</td>
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<td>Bokkel Huinink et al</td>
<td>2/5</td>
<td>Phase III, multicentre, randomised trial. ITT</td>
<td>GEM 1250 mg/m² (27 patients); CDDP 80 mg/m² with VP-16 80 mg/m² (26 patients)</td>
<td>Stage IIIb or IV NSCLC, Supported by Bristol-Myers Squibb</td>
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<td>Colleoni et al</td>
<td>3/5</td>
<td>Phase III, multicentre, randomised trial. ITT</td>
<td>GEM 1000 mg/m² with CDDP 100 mg/m² (166 patients); CDDP 100 mg/m² (166 patients)</td>
<td>Locally advanced or metastatic NSCLC, Supported by Bristol-Myers Squibb</td>
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<td>Vinorelbine</td>
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<td>Baldini et al</td>
<td>3/5</td>
<td>Phase II, multicentre, randomised study. ITT</td>
<td>CDDP 80 mg/m² with VDS 3 mg/m² and MITO 6 mg/m² (49 patients); CDDP 80 mg/m² with IFOS 3 mg/m² with VNB 25 mg/m² (48 patients); CBDC 350 mg/m² with VNB 25 mg/m² (43 patients)</td>
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<td>Colbeeni et al</td>
<td>2/5</td>
<td>Phase II, randomised trial. ITT</td>
<td>CDDP 100 mg/m² with MITO 8 mg/m² and VNB 25 mg/m² (26 patients); CBDC 400 mg/m² with VNB 25 mg/m² (26 patients)</td>
<td>Stage IIIb and IV NSCLC, None stated</td>
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<td>Calucchi et al</td>
<td>3/5</td>
<td>Phase III, multicentre, randomised study. ITT</td>
<td>Two step treatment arms – CDDP 100 mg/m² with VNB 25 mg/m², followed by IFOS 2.5 g/m² and EPi 100 mg/m² (53 patients); IFOS 2.5 g/m² and EPi 100 mg/m², followed by CDDP 100 mg/m² and VNB 25 mg/m² (47 patients)</td>
<td>Stage IIIA/B and IV NSCLC, None stated</td>
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<td>Comella et al</td>
<td>3/5</td>
<td>Phase III, multicentre, randomised trial. ITT</td>
<td>CDDP 40 mg/m² with VP-16 100 mg/m² (52 patients); CBDC 250 mg/m² with CDDP 30 mg/m², VP-16 100 mg/m² and VNB 30 mg/m² (52 patients)</td>
<td>Stage IIIb or IV NSCLC, None stated</td>
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<td>Crawford et al</td>
<td>3/5</td>
<td>Phase III, multicentre, randomised trial. ITT</td>
<td>VNB 30 mg/m² (143 patients); 5-FU 425 mg/m² with LV 20 mg/m² (68 patients)</td>
<td>Stage IV NSCLC, Supported by Glaxo Wellcome</td>
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<td>Deperi et al</td>
<td>3/5</td>
<td>Phase III, multicentre, randomised trial. ITT</td>
<td>VNB 30 mg/m² (119 patients); VNB 30 mg/m² with CDDP 80 mg/m² (121 patients)</td>
<td>Stage IIIa/B or IV NSCLC, Supported by Pierre Fabre</td>
</tr>
<tr>
<td>Furuse et al</td>
<td>3/5</td>
<td>Phase II, crossover, multicentre, randomised trial. ITT</td>
<td>(VNB arm) VNB 25 mg/m² (103 patients) with non-responders switching to VDS 3 mg/m² + CDDP 80 mg/m²; (VDS arm) VDS 3 mg/m² (101 patients) with non-responders switching to VNB 20 mg/m² + CDDP 80 mg/m²</td>
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<td>Le Chevalier et al</td>
<td>2/5</td>
<td>Phase II, international, multicentre, randomised trial. ITT</td>
<td>VNB 30 mg/m² with CDDP 120 mg/m² (206 patients); VDS 3 mg/m² with CDDP 120 mg/m² (200 patients); VNB 30 mg/m² (206 patients)</td>
<td>Stage III or IV NSCLC, Supported by Pierre Fabre</td>
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<tr>
<td>Loruso et al</td>
<td>2/5</td>
<td>Phase III, multicentre, randomised trial. Not ITT</td>
<td>VNB 25 mg/m² (35 patients); VNB 25 mg/m² with CDDP 80 mg/m² (34 patients)</td>
<td>Inoperable NSCLC, None stated</td>
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<td>Jadad quality score: 2/5</td>
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receiving 100 mg/m² docetaxel, necessitating a reduction in dose to 75 mg/m².

Clinical effectiveness of gemcitabine
Two of the six RCTs assessing gemcitabine used cisplatin and etoposide as comparators, while the other four RCTs compared gemcitabine and BSC with BSC alone, gemcitabine with etoposide, gemcitabine and cisplatin with cisplatin, and gemcitabine and cisplatin with mitomycin, ifosfamide and cisplatin (table 1). Gemcitabine (8.7 months, 95% CI 7.7 to 10.2) was shown to have a statistically significant benefit on the median survival of patients compared with etoposide (7.2 months, 95% CI 6.1 to 9.8; p<0.005) and when combined with cisplatin (9.1 months, 95% CI 8.3 to 10.6) compared with cisplatin alone (7.6 months, 95% CI 6.5 to 8.2; p<0.005; table 2). Sustained improvements in measures of quality of life occurred significantly more frequently in patients receiving gemcitabine and BSC than in those treated with BSC alone (22% v 9%, p<0.005). Statistically significant changes to particular elements of the quality of life measures were evident (table 3). Patients receiving gemcitabine and cisplatin had significant improvements in chest pain (p<0.05), while those receiving mitomycin, ifosfamide and cisplatin (p<0.001) or etoposide (significance not stated) had significantly worse alopecia. Adverse effects associated with gemcitabine differed little from the other drug comparators, but included grade 3 and 4 anaemia, neutropenia, thrombocytopenia, hair loss, nausea, infection, and diarrhoea.

Clinical effectiveness of paclitaxel
Six RCTs (table 1) compared the clinical effectiveness of paclitaxel separately with merbarone and piroxantrone, as well as in several combinations including paclitaxel and cisplatin compared with etoposide with cisplatin, paclitaxel and BSC with BSC, paclitaxel and cisplatin with teniposide and cisplatin, paclitaxel and cisplatin against cisplatin. Paclitaxel and BSC (6.8 months, 95% CI 5.7 to 10.2) were associated with statistically significant improvements in median survival compared with cisplatin (4.8 months, 95% CI 3.7 to 6.8; p<0.05, table 2). One and two year survival was improved for patients receiving paclitaxel and BSC compared with cisplatin. Although only the comparison between paclitaxel and BSC (95% CI 20 to 41) with BSC (95% CI 18 to 39) was statistically significant. Of the four RCTs examining the effects of paclitaxel on quality of life (table 3), two found a significant beneficial effect on functional ability for patients receiving paclitaxel and BSC compared with BSC alone (p<0.05) and for paclitaxel and cisplatin compared with teniposide and cisplatin (fatigue p<0.01, appetite loss p<0.001). Adverse events, whether haematological or non-haematological, differed depending on the interventions compared. Three RCTs assessing paclitaxel with merbarone and piroxantrone, paclitaxel and cisplatin with cisplatin alone, and paclitaxel and BSC with BSC only found that severe adverse effects were more frequent in patients receiving paclitaxel. In contrast, two of three RCTs comparing paclitaxel and cisplatin with teniposide and cisplatin showed severe adverse effects to be more evident in those on teniposide and cisplatin. Adverse effects associated with paclitaxel included thrombocytopenia, leukaemia, anaemia, alopecia, and nausea/vomiting.

Clinical effectiveness of vinorelbine
Thirteen RCTs assessed 12 different comparisons of vinorelbine in combination with and in contrast to other interventions (table 1). Five RCTs compared different doses of vinorelbine and/or different combinations. Two RCTs used a form of crossover design, although patients in one RCT only changed interventions when considered non-responders. Different combinations of vinorelbine were used in the RCTs...
Table 2  Summary of evidence of effect of docetaxel, gemcitabine, paclitaxel and vinorelbine on patient survival

<table>
<thead>
<tr>
<th>Study details</th>
<th>Patient survival</th>
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<tr>
<td><strong>Docetaxel</strong></td>
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<tr>
<td>Shepherd et al</td>
<td>Median survival: BSC=4.6 months (95% CI 3.7 to 6.0); DOC (both doses)=7 months (95% CI 5.5 to 9.0) [p=0.047]; DOC (100 mg/m²)=5.9 months (p=0.78); DOC (75 mg/m²)=7.5 months (p=0.01)</td>
</tr>
<tr>
<td>Roszkowski et al</td>
<td>Median survival: DOC arm=4.0 months (95% CI 3.0 to 8.0); BSC arm=5.7 months (95% CI 4.4 to 6.8)</td>
</tr>
<tr>
<td>One year survival: BSC=19%; DOC (both doses)=29%; DOC (100 mg/m²)=19%; DOC (75 mg/m²)=37%; BSC=12%</td>
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<tr>
<td>Two year survival: DOC=25%; BSC=16%</td>
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<tr>
<td>One year survival: DOC=12%; BSC=0%</td>
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<tr>
<td><strong>Gemcitabine</strong></td>
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<tr>
<td>Anderson et al</td>
<td>Median survival: GEM+BSC=5.7 months (95% CI 4.6 to 7.6); BSC=5.9 months (95% CI 5.0 to 7.9)</td>
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<tr>
<td>Estimated one year survival: GEM+BSC=25%; BSC=22%</td>
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<td><strong>Paclitaxel</strong></td>
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<tr>
<td>Bonani et al</td>
<td>Median survival: CDDP+VP-16 arm=7.6 months; PAX (250 mg/m²)+CDDP=10 months; PAX (135 mg/m²)+CDDP=9.5 months</td>
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<tr>
<td>One year survival: PAX+VP-16 arm=31.8%; PAX (250 mg/m²)+CDDP=40.3%; PAX (135 mg/m²)+CDDP=37.4%; BSC=7%</td>
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<td><strong>Vinorelbine</strong></td>
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<tr>
<td>Baldini et al</td>
<td>Median survival: CDDP+MITO+VDS=8.4 months; CDDP+IFOS+VNB=8.8 months; CBDCA+VNB=7.9 months</td>
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<tr>
<td>One year survival: CDDP+MITO+VDS=18%; CDDP+IFOS+VNB=15%; CBDCA+VNB=16%</td>
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<tr>
<td>Colleoni et al</td>
<td>Median survival: CDDP+MITO+VNB=9.9 months (range 3-14); CBDCA+VNB=8.8 months (range 1-18)</td>
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<td>One year survival: not assessed</td>
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<tr>
<td>Colucci et al</td>
<td>Median survival: CDDP+VNB (IFOS+EP)=9 months; IFOS+EP (CDDP+VNB)=7 months (p=NS)</td>
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<tr>
<td>One year survival: not assessed</td>
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<tr>
<td>Comella et al</td>
<td>Median survival: CDDP+VP-16=31 weeks; CBDCA+CDDP+VNB=27 weeks (p=NS)</td>
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<tr>
<td>Crawford et al</td>
<td>Median survival (estimated): VNB=30 weeks; 5FU+LV=22 weeks (p=0.03)</td>
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<tr>
<td>One year survival: VNB=25%; 5FU+LV=16% (p=0.06)</td>
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<tr>
<td>Depierre et al</td>
<td>Median survival: VNB=32 weeks; VNB+CDDP=33 weeks (p=NS)</td>
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<td>One year survival: not assessed</td>
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<tr>
<td>Furuse et al</td>
<td>Median survival: VNB arm=52.4 weeks; VDS arm=43.6 weeks (p=NS)</td>
</tr>
<tr>
<td>One year survival: not assessed</td>
<td></td>
</tr>
<tr>
<td>Le Chevalier et al</td>
<td>Median survival: VNB+CDDP=40 weeks; VDS+CDDP=32 weeks (p=0.09); VNB=31 weeks (p=0.05)</td>
</tr>
<tr>
<td>One year survival: not assessed</td>
<td></td>
</tr>
<tr>
<td>Lorusso et al</td>
<td>Median survival: VNB=30 weeks; VNB+CDDP=38 weeks (p=NS)</td>
</tr>
<tr>
<td>One year survival: not assessed</td>
<td></td>
</tr>
<tr>
<td>Martoni et al</td>
<td>Median survival: EPI+CDDP=10.5 months (95% CI 9.4 to 11.5); VNB+CDDP=9.6 months (95% CI 8.4 to 10.8)</td>
</tr>
<tr>
<td>One year survival: EPI+CDDP=42%; VNB+CDDP=39% (p=NS)</td>
<td></td>
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<tr>
<td>Perol et al</td>
<td>Median survival: CDDP+MITO+VDS=33.4 weeks (p=NS)</td>
</tr>
<tr>
<td>Two year survival: CDDP+MITO+VDS=48 weeks (p=NS)</td>
<td></td>
</tr>
<tr>
<td>Wozniak et al</td>
<td>Median survival: CDDP+MITO+VDS=8 months (p=0.01)</td>
</tr>
<tr>
<td>One year survival: VNB+CDDP=36%; CDDP=20%</td>
<td></td>
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<tr>
<td>Two year survival: VNB+CDDP=12%; CDDP=6%</td>
<td></td>
</tr>
<tr>
<td><strong>Elderly Lung Cancer VNB Italian Study Group</strong></td>
<td>Median survival: VNB=28 weeks; BSC=21 weeks</td>
</tr>
<tr>
<td>6 month survival: VNB=55%; BSC=41%</td>
<td></td>
</tr>
<tr>
<td>One year survival: VNB=32%; BSC=14%</td>
<td></td>
</tr>
<tr>
<td><strong>Combined regimens</strong></td>
<td></td>
</tr>
<tr>
<td>Comella et al</td>
<td>Median survival: CDDP+GEM+VNB=50 weeks (95% CI 41 to 58); CDDP+IFOS+VDS+LON=33 weeks (95% CI 24 to 41)</td>
</tr>
<tr>
<td>One year survival: CDDP+GEM+VNB=48%; CDDP+IFOS+VDS+LON=29%</td>
<td></td>
</tr>
<tr>
<td>Two year survival: CDDP+GEM+VNB=19%; CDDP+IFOS+VDS+LON=0%</td>
<td></td>
</tr>
<tr>
<td>Comella et al</td>
<td>Median survival: CDDP+GEM+VNB=51 weeks; CDDP+GEM=42 weeks; CDDP+VNB=35 weeks</td>
</tr>
<tr>
<td>One year survival: CDDP+GEM+VNB=45%; CDDP+GEM=40%; CDDP+VNB=34%</td>
<td></td>
</tr>
<tr>
<td>Kaminski et al</td>
<td>Median survival: not assessed</td>
</tr>
<tr>
<td>One year survival: not assessed</td>
<td></td>
</tr>
<tr>
<td>Perry et al</td>
<td>Median survival: PAX+IFOS=8.5 months; VNB+IFOS=7.4 months (95% CI 5.3 to 13.3)</td>
</tr>
<tr>
<td>One year survival (estimated): PAX+IFOS=35% (95% CI 24; 52%); VNB+IFOS=38% (95% CI 26 to 55%)</td>
<td></td>
</tr>
<tr>
<td>Frasci et al</td>
<td>Median survival: GEM+VNB=29 wks; VNB=18 weeks</td>
</tr>
<tr>
<td>Six month survival: estimated: GEM+VNB=56%; VNB=32%</td>
<td></td>
</tr>
<tr>
<td>One year survival (estimated): GEM+V NB=30%; VNB=13%</td>
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</tbody>
</table>

BSC=best supportive care; CBDCA=carboplatin; CDDP=cisplatin; DOC=docetaxel; EPI=epirubicin; GEM=gemcitabine; IFOS=ifosfamide; ITT=intention to treat; LON=lonidamine; LV=leucovorin; MER=merbarone; MITO=mitomycin; NSCLC=non-small cell lung cancer; PAX=paclitaxel; PX=piparoxantrone; VDS=vindesine; VM=26-teniposide; VNB=vinorelbine; VP-16=etoposide; 5FU=fluorouracil.
including vinorelbine alone; vinorelbine and cisplatin; vinorelbine and carboplatin; vinorelbine, carboplatin and cisplatin; vinorelbine, mitomycin and cisplatin; vinorelbine, ifosfamide; vinorelbine, cisplatin, ifosfamide and epirubicin; and vinorelbine, cisplatin, carboplatin and etoposide.

One RCT concentrated on elderly patients aged over 70 years. Of the 11 RCTs showing improvement in median survival for patients receiving vinorelbine in differing combinations, 16–18, 22, 24–26, 33–37, the comparisons of vinorelbine with fluorouracil and leucovorin (30 weeks vs 22 weeks, p < 0.05) and vinorelbine and cisplatin with cisplatin (8 months vs 6 months, p < 0.005) showed statistically significant increases in survival (table 2). 22 Patient survival to 1 and 2 years was assessed in six RCTs with none showing a significant difference between the combinations of interventions. 16–18, 33–37 The effect of vinorelbine on quality of life was assessed in three RCTs (table 3), 34, 36, 37 although only the comparison between vinorelbine and BSC showed any statistically significant difference. 36 Patients receiving vinorelbine experienced significant improvements in cognitive function (p < 0.05), dyspnoea (p < 0.05), and pain medication (p < 0.01), but significantly worse in constipation (p < 0.005), peripheral neuropathy (p < 0.05), and hair loss (p < 0.001). Adverse events, including constipation, heart toxicity, leukopenia, neutropenia, vomiting and alopecia, varied with the different combinations compared. Only two RCTs found any significant variation. 22 When compared with vinorelbine and cisplatin, patients receiving epirubicin and cisplatin suffered significantly more leukopenia (p < 0.01), thrombocytopenia (p < 0.05), and alopecia (p < 0.001). 38 Patients receiving vinorelbine, mitomycin, and cisplatin suffered significantly more anaemia (p < 0.01), neutropenia (p < 0.01), sepsis (p < 0.05), and local reaction (p < 0.05) than those receiving vindesine, mitomycin, and cisplatin. 39 In addition, five patients stopped treatment because of severe toxic events in the comparison of vinorelbine with BSC. 40

### Clinical effectiveness of other combined treatments

Of the five RCTs assessing the clinical effectiveness of combined treatments, two compared cisplatin, gemcitabine and vinorelbine with either cisplatin epirubicin, vindesine and lonidamine 19 or cisplatin and gemcitabine and cisplatin and vinorelbine (table 1). 41 Other RCTs compared paclitaxel and ifosfamide with vinorelbine and ifosfamide, 42 gemcitabine and vinorelbine with vinorelbine, 43 and paclitaxel and carboplatin with paclitaxel and gemcitabine. 42 Only the combination of cisplatin, gemcitabine and vinorelbine (50 weeks, 95% CI 41 to 58) compared with cisplatin, epirubicin, vindesine and lonidamine (33 weeks, 95% CI 24 to 41) was associated with a statistically significant increase in median survival (table 2). 41 Assessment of the effects on quality of life was limited, with none of the combined treatments affecting quality of life (table 3). 44–46, 48 Adverse effects varied with the components of the combined treatments, although no significant differences were evident. 45–48

### The lung cancer costing model

The results are presented in terms of incremental cost per life year saved (tables 4 and 5) using the synthesis of trial data to give a broad picture of likely relative cost effectiveness compared with BSC. Only the single new agents and their combination with cisplatin have been considered. BSC is the comparator v which remains standard treatment for most patients in the UK. Caution should be used in any comparison of regimens because of the way the data were combined (described above) and the lack of direct comparisons.

#### Table 3 Summary of evidence of effect of docetaxel, gemcitabine, paclitaxel and vinorelbine on quality of life

<table>
<thead>
<tr>
<th>Study details</th>
<th>Quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td></td>
</tr>
<tr>
<td>Shephard et al 49</td>
<td>GQ parameters favoured DOC patients, significant differences for pain (p = 0.006), fatigue (p = 0.06) and tumour related medications used (p = 0.02)</td>
</tr>
<tr>
<td>Roszkowski et al 40</td>
<td>DOC had significantly favourable effects on emotional functioning (p &lt; 0.05), nausea/vomiting (p = 0.04), pain (p &lt; 0.0001) and dyspnoea (p = 0.02). No difference between global health status and physical functioning scores (p = NS).</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td></td>
</tr>
<tr>
<td>Anderson et al 51</td>
<td>On SS14 symptom scale GEM+BSC patients improved (10%) from baseline to 2 months compared with deterioration in BSC patients (+1% p = 0.113). Sustained (4-weeks) improvement (25%) in SS14 score was significantly higher for patients on GEM+BSC (22%) compared with BSC (9%) (p = 0.005).</td>
</tr>
<tr>
<td>Bokkel Huinink et al 52</td>
<td>No significant difference in change from baseline on global, physical, role, cognitive, emotional and social aspects of QoL (p = 0.02).</td>
</tr>
<tr>
<td>Cardenal et al 53</td>
<td>No clinically significant differences in change from baseline within treatment arm or between treatment arms in functional domains or global QoL. Statistically significant difference between treatment arms in change from baseline for alopecia, worse for the VP-16 arm. Pain, insomnia, cough, hemoptysis, chest pain and shoulder pain by GEM and VP-16.</td>
</tr>
<tr>
<td>Crino et al 54</td>
<td>Global QoL did not change significantly in either arm. Comparisons of change from baseline showed a worsening of alopecia in the TriComb arm and a greater improvement in chest pain in the GEM+CDDP arm (p = 0.05).</td>
</tr>
<tr>
<td>Sandler et al 55</td>
<td>No significant differences in QoL between treatment arms in change from baseline.</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td></td>
</tr>
<tr>
<td>Bonomi et al 56</td>
<td>No significant difference between treatment arms in change from baseline.</td>
</tr>
<tr>
<td>Ranson et al 57</td>
<td>No statistically significant difference between arms in change from baseline.</td>
</tr>
<tr>
<td>Gatzemier et al 58</td>
<td>On symptom scales CDDP patients had significant worsening of nausea and vomiting (p &lt; 0.0003), appetite loss (p = 0.02) and constipation (p = 0.03), while PA+X+CDDP patients had significant worsening of hair loss and peripheral neuropathy (p &lt; 0.0001).</td>
</tr>
<tr>
<td>Giaccone et al 59</td>
<td>Patients on PA+X+CDDP had significant beneficial effects on functional scales and some symptom scales at 6 weeks (fatigue (p = 0.006) and appetite loss (p = 0.01)), which disappeared at 12 weeks.</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td></td>
</tr>
<tr>
<td>Crawford et al 60</td>
<td>No significant difference between treatment arms in change from baseline (no data presented).</td>
</tr>
<tr>
<td>Martino et al 61</td>
<td>No significant change in global QoL.</td>
</tr>
<tr>
<td>ELVIS 62</td>
<td>On EORTC functional and symptom scales and on LC13, VNB had significant improvement in cognitive function (p = 0.02), pain (p = 0.02), dyspnea (p = 0.05), and pain medication (p = 0.01), but significantly worse on constipation (p = 0.002), nausea and vomiting (p = 0.07) peripheral neuropathy (p = 0.04) and hair loss (p = 0.0001).</td>
</tr>
<tr>
<td>Combined treatments</td>
<td></td>
</tr>
<tr>
<td>Comella et al 63</td>
<td>Improved QoL, score CDDP-GEM+VNB=59%, CDDP+EP+VDS+ LON=39% (p not stated)</td>
</tr>
<tr>
<td>Frasci et al 64</td>
<td>Almost 60% of GEM+VNB patients did not show impairment of QoL during treatment, compared to approximately 40% in the VNB arm. Insufficient reporting of QoL measures (p not stated).</td>
</tr>
</tbody>
</table>

BSC=best supportive care; CDDP=cisplatin; DOC=docetaxel; EPI=epirubicin; GEM=gemcitabine; LON=lonidamine; PAX=Paclitaxel; QoL=quality of life; SS14=subset of commonly reported symptoms from the European Organisation for Research and Treatment (EORTC) Quality of Life instrument (EORTC QLQ-C30 and LC13 scales); TriComb=combination of MITO, IFOS and CDDP; VDS=vindesine; VNB=vinorelbine; VP-16=etoposide.
The regimens with the least incremental cost effectiveness over BSC under the baseline scenario are vinorelbine, vinorelbine+cisplatin, and gemcitabine. These regimens retain their cost effectiveness under a range of assumptions and may even be dominant under certain circumstances. The gemcitabine and vinorelbine regimens deliver similar levels of cost effectiveness if the same number of cycles and cycle length are applied. However, the results also show the reasonable cost effectiveness of gemcitabine+cisplatin and the paclitaxel+cisplatin regimens compared with BSC throughout a range of scenarios and assumptions. The (unlicensed) paclitaxel and docetaxel single agents remain relatively expensive compared with BSC. Docetaxel appears to be relatively expensive as second line treatment in the baseline scenario because of its small survival gain over BSC, but would be prescribed for only small numbers of patients.

Costs in routine care would probably be much lower than those based on data from trials. In the trials patients would be given chemotherapy as per the protocol if they could tolerate it, whereas in routine care physicians and patients would review continuation on a course by course basis, with chemotherapy being stopped in those whose tumours did not respond. This would make chemotherapy much more cost effective (see line 3, table 5).

**DISCUSSION**

Evidence of clinical effectiveness appeared to be of reasonable quality given the difficulties associated with blinding many of the treatments. Gemcitabine, paclitaxel, and vinorelbine as first line treatment and docetaxel as second line treatment appear to be beneficial to patient survival and to quality of life, particularly when used as combined treatments. Although improvements in median survival tend to be relatively small, ranging from 2 to 4 months, these appear worthwhile given that survival for untreated patients tends to be limited to ranging from 2 to 4 months, these appear worthwhile given the difficulties associated with blinding many of the treatments. Gemcitabine, paclitaxel, and vinorelbine as first line treatment and docetaxel as second line treatment appear to be beneficial to patient survival and to quality of life, particularly when used as combined treatments. Although improvements in median survival tend to be relatively small, ranging from 2 to 4 months, these appear worthwhile given that survival for untreated patients tends to be limited to
about 5 months. Importantly, these gains in survival are not at the expense of quality of life which appears to have improved compared with BSC or the older chemotherapy agents.

Vinorelbine, paclitaxel, vinorelbine and gemcitabine appear to have the least incremental cost relative to BSC, taking into account both survival gains and quality of life. Were higher levels of funding available, the increased survival offered by the gemcitabine+cisplatin and paclitaxel+cisplatin regimens could be favoured. However, given the opportunity of informed choice, not all patients would wish to undergo treatment other than for palliative care. For example, a survey of 81 patients by Silvestri et al reported that patients would not want chemotherapy unless median survival improved by 4.5 months for mild toxicity and 9.0 months for severe toxicity. However, 90% of our expert reviewers reported a lack of understanding by patients on the effects and side effects of chemotherapy, noting a general belief that the side effects of such treatments outweigh any benefits. It was not possible to present results by disease stage given the lack of subgroup analysis in the reporting of survival data, although the majority of patients were stage IV.

Consistent methods for undertaking systematic reviews were applied throughout the review, with support from an expert advisory group including clinicians, patient representatives, and academics. Possible limitations were lack of follow-up with authors to clarify study details, use of the Jadad scale for assessing methodological quality when it may more accurately reflect how well a study was reported, and lack of a validated method for assessing the methodological quality of quality of life studies.

Possible inadequacies in individual studies may undermine the evidence of effectiveness. Although nearly half of the studies examined quality of life as a primary or secondary outcome, very few evaluated it adequately, limiting accurate assessment of clinical and cost effectiveness. Studies provided limited information on patient characteristics, affecting any assessment among different patient subgroups or the generalisability of findings to patients referred in practice. Some studies failed to report results using intention to treat analysis which, when coupled with the high attrition of patients, creates the opportunity for bias. Several studies were either sponsored or undertaken by the manufacturers of the drugs which may bring into question their independence and lead to fears of bias.

The new drugs represent a worthwhile but still very modest advance, with no cure and a gain in survival of only a few months. However, when valuing short durations of life, it has been argued that the concept of diminishing marginal utility creates the opportunity for bias. Several studies were either sponsored or undertaken by the manufacturers of the drugs which may bring into question their independence and lead to fears of bias.

In conclusion, although the clinical benefits from docetaxel, gemcitabine, paclitaxel and vinorelbine appear relatively small, their benefit to patients with lung cancer appears to be worthwhile and cost effective. With important new evidence emerging, we recommend that our findings are periodically reviewed or revised.

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