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, 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.
Paclitaxel, docetaxel, gemcitabine, and vinorelbine in NSCLC

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 confined 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 Southport 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 aggregated by patient numbers with larger trials thus carrying more weight. It is recognised that this method of pooling consists of indirect comparisons between trials and is therefore open to confounding. There may, for example, be differences in patient populations among trials. In addition, the comparator interventions vary markedly between trials and not all are in current usage. As a consequence, we chose median survival rather than incremental survival. However, the mixture of different patient types may also strengthen the conclusions and generalisability of the model. Although this approach is not the ideal way of directly comparing regimens, it does make the most of the data available, illustrates a range of possible cost effectiveness estimates across a range of assumptions, and can be interpreted with the aid of sensitivity analyses. Best and worst estimates were defined by the upper and lower bounds of individual trial data. Paclitaxel doses (and hence costs) varied markedly between the studies and so several regimens were modelled.

Sensitivity analysis
One way sensitivity analysis was carried out across a range of variables including number of cycles (advice from clinical colleagues was that in routine care a more realistic scenario would be to assume 60% of patients would have only 1–2 cycles while 40% would continue towards the recommended number of cycles: three for gemcitabine, vinorelbine, and docetaxel regimens and four for paclitaxel); number of administrations per cycle of vinorelbine; best and worst cycles from trials; effect of discounts on BNF prices; and cost of newer antiemetic regimens. Mean survival estimates calculated from single studies by Berthelot et al. and non-patient based utility estimates were also examined. The cost of BSC, particularly the number of inpatient days (21 versus 19 days), was varied to reflect slight differences between sources.

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,17–23 six gemcitabine,13,14,28–33 six paclitaxel,14,17–23,34–46 13 vinorelbine,14,20–27 and five combined treatments.47–50 The characteristics of these studies are presented in table 1.

Five RCTs were judged to be of good quality (Jadad score ≥2/3 or ≥4/5), 10 of adequate quality (Jadad score 3/5), and 18 of poor quality (Jadad score ≤2/5). Twenty RCTs lacked an adequate description of randomisation,17–23,26–28,30,32 although for 18 this was difficult given the comparator (for example, BSC).14,17–19,21,22,34–36 and one did not describe withdrawals.22 Of the 33 RCTs, 15 stated that they were supported by or involved industry—two for docetaxel,17–19 four for gemcitabine,14,17–19,21,22,34–36 three for paclitaxel,14,20–27 and six for vinorelbine.14,20–27,36–40,44–46.

Clinical effectiveness of docetaxel
Of the three RCTs (table 1), two compared docetaxel with BSC as either first19 or second line treatment,17 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 vs BSC 4.6 months, p=0.01). 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). When used as second line treatment, docetaxel had a significant beneficial effect on pain (p<0.01). 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>
<thead>
<tr>
<th>Study details</th>
<th>Design</th>
<th>Intervention</th>
<th>Subjects</th>
<th>Conflicts of interest</th>
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</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td></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</td>
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<tr>
<td>Shepherd et al</td>
<td>Jadad quality score: 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>
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<tr>
<td>Roszkowski et al</td>
<td>Jadad quality score: 2/3</td>
<td>Phase III, open-label, multicentre, randomised trial. ITT</td>
<td>Second line treatment: DOC 100 mg/m² (125 patients); VNB or IFOS (123 patients)</td>
<td>NSCLC stage IIIB/IV</td>
</tr>
<tr>
<td>Fossella et al</td>
<td>Jadad quality score: 2/5</td>
<td>Multicentre, randomised trial. ITT</td>
<td>GEM 1000 mg/m² with BSC (150 patients); BSC (150 patients)</td>
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<td>Phase II, multicentre, open-label, randomised trial. Not ITT</td>
<td>Phase III, multicentre, randomised trial. 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</td>
</tr>
<tr>
<td>Jadad quality score: 2/5</td>
<td>Phase II, multicentre, randomised trial. ITT</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</td>
</tr>
<tr>
<td>Jadad quality score: 3/5</td>
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<td>Phase II, 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 III (A or B) or IV NSCLC</td>
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<tr>
<td>Jadad quality score: 2/5</td>
<td>Phase III, multicentre, randomised trial. ITT</td>
<td>Phase II, 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 IIIB or IV NSCLC</td>
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<td>Jadad quality score: 1/5</td>
<td>Phase III, multicentre, randomised trial. ITT</td>
<td>Phase II, randomised trial. Not 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)</td>
<td>Stage IIIB or IV NSCLC</td>
</tr>
<tr>
<td>Jadad quality score: 2/5</td>
<td>Phase II, randomised study. Not ITT</td>
<td>Phase III, multicentre, randomised trial. ITT</td>
<td>CDDP 100 mg/m² with MITO 8 mg/m² and VNB 25 mg/m² (26 patients); CBDCA 350 mg/m² with VNB 25 mg/m² (43 patients)</td>
<td>Stage IIIB and IV NSCLC</td>
</tr>
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<td>Jadad quality score: 2/3</td>
<td>Phase III, multicentre, randomised trial. ITT</td>
<td>Phase II, multicentre, randomised trial. ITT</td>
<td>CBDP 40 mg/m² with VP-16 80 mg/m² (35 patients); CDDP 100 mg/m² with VNB 25 mg/m² (43 patients)</td>
<td>Stage IIIB or IV NSCLC</td>
</tr>
<tr>
<td>Jadad quality score: 2/5</td>
<td>Phase II, multicentre, randomised trial. ITT</td>
<td>Phase II, multicentre, randomised trial. ITT</td>
<td>CDDP 40 mg/m² with VP-16 100 mg/m² (53 patients); CBDCA 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</td>
</tr>
<tr>
<td>Jadad quality score: 3/5</td>
<td>Phase II, multicentre, randomised trial. ITT</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 IIIB or IV NSCLC</td>
</tr>
<tr>
<td>Jadad quality score: 3/5</td>
<td>Phase II, randomised trial. ITT</td>
<td>Phase III, multicentre, randomised trial. ITT</td>
<td>VNB 30 mg/m² with CDDP 80 mg/m² (120 patients); VNB 30 mg/m² (200 patients); VNB 30 mg/m² (206 patients)</td>
<td>Stage IIIB or IV NSCLC</td>
</tr>
<tr>
<td>Jadad quality score: 3/5</td>
<td>Phase II, crossover, multicentre, randomised trial. ITT</td>
<td>Phase II, multicentre, randomised trial. ITT</td>
<td>VNB 25 mg/m² (103 patients) with non-responders switching to VDS 3 mg/m²+CDDP 80 mg/m²; VDS 3 mg/m² (101 patients) with non-responders switching to VNB 20 mg/m²+CDDP 80 mg/m²</td>
<td>Stage IIIB or IV NSCLC</td>
</tr>
<tr>
<td>Jadad quality score: 3/5</td>
<td>Phase II, international, multicentre, randomised trial. ITT</td>
<td>Phase III, 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</td>
</tr>
</tbody>
</table>
| Jadad quality score: 3/5 | Phase II, international, multicentre, randomised trial. ITT | Phase III, multicentre, randomised trial. ITT | VNB 25 mg/m² (35 patients); VNB 25 mg/m² with CDDP 80 mg/m² (34 patients) | Inoperable NSCLC | None stated
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<0.05) 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 BSC (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, 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 (4.8 months, 95% CI 3.7 to 6.8; p<0.05, table 2). 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 receiving 100 mg/m² docetaxel, necessitating a reduction in dose to 75 mg/m².

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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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docetaxel</strong></td>
<td></td>
</tr>
<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). One year survival: BSC=19%; DOC (both doses)=29%; DOC (100 mg/m²)=19%; DOC (75 mg/m²)=37%; BSC=12%.</td>
</tr>
<tr>
<td><strong>Gemcitabine</strong></td>
<td></td>
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<tr>
<td>Anderson et al</td>
<td>Median survival: GEM=5.7 months (95% CI 4.6 to 7.6); BSC=5.9 months (95% CI 5.0 to 7.9)</td>
</tr>
<tr>
<td><strong>Paclitaxel</strong></td>
<td></td>
</tr>
<tr>
<td>Bonomi et al</td>
<td>Median survival: CDDP+VP-16=7.6 months (95% CI 5.4 to 9.3)</td>
</tr>
<tr>
<td><strong>Vinorelbine</strong></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td><strong>Combined treatments</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+EPI+VDS+LON=33 weeks (95% CI 24 to 41)</td>
</tr>
</tbody>
</table>

BSC=best supportive care; CBDCA=carboplatin; CDDP=cisplatin; DOC=docetaxel; EPI=epirubicin; GEM=gemcitabine; IFOS=ifosfamide; ITT=intention to treat; LON=lovastatin; LV=leucovorin; MITO=mitomycin; NICE=non-small cell lung cancer; PAX=paclitaxel; PAX+CDDP=8.8 months; PAX (250 mg/m²)+CDDP=40.3%; PAX (135 mg/m²)+CDDP=37.4%. Six month survival (estimated): GEM+CDDP=30%; CDDP+EPI+VDS+LON=29%.

**Gemcitabine**

Anderson et al 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)

**Paclitaxel**

Bonomi et al Median survival: CDDP+VP-16=7.6 months; PAX (250 mg/m²)+CDDP=10 months; PAX (135 mg/m²)+CDDP=9.5 months

**Vinorelbine**

Baldini et al Median survival: CDDP+MITO+VDS=8.4 months; CDDP+IFOS+VNB=8.8 months; CBDCA+VNB=7.9 months

**Combined treatments**

Comella et al Median survival: CDDP+GEM+VNB=50 weeks (95% CI 41 to 58); CDDP+EPI+VDS+LON=33 weeks (95% CI 24 to 41)

BSC=best supportive care; CBDCA=carboplatin; CDDP=cisplatin; DOC=docetaxel; EPI=epirubicin; GEM=gemcitabine; IFOS=ifosfamide; ITT=intention to treat; LON=lovastatin; LV=leucovorin; MITO=mitomycin; NICE=non-small cell lung cancer; PAX=paclitaxel; PAX+CDDP=8.8 months; PAX (250 mg/m²)+CDDP=40.3%; PAX (135 mg/m²)+CDDP=37.4%. Six month survival (estimated): GEM+CDDP=30%; CDDP+EPI+VDS+LON=29%.
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.\textsuperscript{43} Of the 11 RCTs showing improvement in median survival for patients receiving vinorelbine in differing combinations,\textsuperscript{18,44-46,48-50} the comparisons of vinorelbine with fluorouracil and leucovorin (30 weeks v 22 weeks, p<0.05) and vinorelbine and cisplatin (8 months v 6 months, p<0.005) showed statistically significant increases in survival (table 2).\textsuperscript{6,7,19} Patient survival to 1 and 2 years was assessed in six RCTs with none showing a significant difference between the combinations of interventions.\textsuperscript{18,44,46,48,49,51,52} The effect of vinorelbine on quality of life was assessed in three RCTs (table 3),\textsuperscript{43,45,46} although only the comparison between vinorelbine and BSC showed any statistically significant difference.\textsuperscript{43} Patients receiving vinorelbine experienced significant improvements in cognitive function (p<0.05), dyspnoea (p=0.05), and pain medication (p=0.01), but significantly worsened 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.\textsuperscript{43,46} 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). 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.\textsuperscript{43} In addition, five patients stopped treatment because of severe toxic events in the comparison of vinorelbine with BSC.\textsuperscript{19}

### 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\textsuperscript{16} or cisplatin and gemcitabine and cisplatin and vinorelbine (table 1).\textsuperscript{43} Other RCTs compared paclitaxel and ifosfamide with vinorelbine and ifosfamide,\textsuperscript{11} gemcitabine and vinorelbine with vinorelbine,\textsuperscript{47} and paclitaxel and carboplatin with paclitaxel and gemcitabine.\textsuperscript{12} 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).\textsuperscript{7} Assessment of the effects on quality of life was limited, with none of the combined treatments affecting quality of life (table 3).\textsuperscript{43-46,51} Adverse effects varied with the components of the combined treatments, although no significant differences were evident.\textsuperscript{45,51}

### 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 as this 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.
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 quality given the difficulties associated with blinding many of the treatments. Gemcitabine, paclitaxel, and vinorelbine as single agents remain relatively effective as second line treatments 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 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 the lower BSC estimate (£2200) as compared with the cost of the alternative treatment.

### Table 4  Cost effectiveness results†

<table>
<thead>
<tr>
<th></th>
<th>BSC</th>
<th>GEM</th>
<th>GEM+CDDP</th>
<th>VNB</th>
<th>VNB+CDDP</th>
<th>PAX (135)+CDDP</th>
<th>PAX (175)+CDDP</th>
<th>PAX (250)+CDDP</th>
<th>DOC</th>
<th>DOC (2L)</th>
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<td>Median no of cycles</td>
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<td>5</td>
<td>11</td>
<td>7</td>
<td>13</td>
<td>14</td>
<td>19</td>
<td>21</td>
<td>7</td>
<td>4</td>
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<tr>
<td>No. of administrations (GEM, VNB, etc)</td>
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<td>3</td>
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<td>9</td>
<td>12</td>
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<td>Drug cost (GEM,VNB, etc) (£)</td>
<td>2637</td>
<td>3516</td>
<td>2140</td>
<td>2140</td>
<td>6858</td>
<td>4364</td>
<td>5610</td>
<td>6483</td>
<td>3975</td>
<td>3300</td>
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<td>Drug cost (CDDP) (£)</td>
<td>243</td>
<td>219</td>
<td>243</td>
<td>243</td>
<td>243</td>
<td>243</td>
<td>243</td>
<td>243</td>
<td>204</td>
<td></td>
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<tr>
<td>Administration/side effects/chem counselling (£)</td>
<td>1495</td>
<td>2562</td>
<td>1823</td>
<td>2377</td>
<td>1435</td>
<td>1696</td>
<td>1696</td>
<td>1460</td>
<td>1065</td>
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<tr>
<td>Average cost per patient (£)</td>
<td>3342</td>
<td>4312</td>
<td>6321</td>
<td>3963</td>
<td>4736</td>
<td>7823</td>
<td>6304</td>
<td>7550</td>
<td>8147</td>
<td>5040</td>
</tr>
<tr>
<td>Incremental cost (v BSC) (£)</td>
<td>789</td>
<td>2979</td>
<td>620</td>
<td>1394</td>
<td>4951</td>
<td>2962</td>
<td>4208</td>
<td>4804</td>
<td>1698</td>
<td>1023</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>5.24</td>
<td>6.90</td>
<td>8.80</td>
<td>7.06</td>
<td>8.45</td>
<td>6.51</td>
<td>9.40</td>
<td>8.31</td>
<td>10.00</td>
<td>6.00</td>
</tr>
<tr>
<td>Life years saved (LYS)</td>
<td>0.44</td>
<td>0.58</td>
<td>0.73</td>
<td>0.59</td>
<td>0.70</td>
<td>0.54</td>
<td>0.78</td>
<td>0.73</td>
<td>0.83</td>
<td>0.50</td>
</tr>
<tr>
<td>Average cost per LYS (£)</td>
<td>7658</td>
<td>7184</td>
<td>8623</td>
<td>6738</td>
<td>6723</td>
<td>3048</td>
<td>10281</td>
<td>9776</td>
<td>10081</td>
<td>8824</td>
</tr>
<tr>
<td>Incremental median survival (months) (v BSC)</td>
<td>1.66</td>
<td>3.56</td>
<td>1.82</td>
<td>3.21</td>
<td>1.27</td>
<td>4.16</td>
<td>3.58</td>
<td>4.76</td>
<td>0.70</td>
<td>0.70</td>
</tr>
<tr>
<td>Incremental LYS (v BSC)</td>
<td>0.14</td>
<td>0.30</td>
<td>0.15</td>
<td>0.27</td>
<td>0.11</td>
<td>0.35</td>
<td>0.30</td>
<td>0.40</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>Incremental cost per LYS (v BSC) (£)</td>
<td>5690</td>
<td>10041</td>
<td>4091</td>
<td>5206</td>
<td>46610</td>
<td>8537</td>
<td>14124</td>
<td>12104</td>
<td>26707</td>
<td>17546</td>
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</tbody>
</table>

BSC=best supportive care; GEM=gemcitabine; VNB=vinorelbine; PAX=paclitaxel; DOC=docetaxel; CDDP=cisplatin; LYS=life years saved; 2L=second line treatment.

*All costs obtained in or converted to 1999/2000 prices.58

### Table 5  Selected one way sensitivity analysis: incremental cost per LYS (£) v BSC

<table>
<thead>
<tr>
<th></th>
<th>GEM</th>
<th>GEM+CDDP</th>
<th>VNB</th>
<th>VNB+CDDP</th>
<th>PAX (135) +CDDP</th>
<th>PAX (175) +CDDP</th>
<th>PAX (250) +CDDP</th>
<th>DOC</th>
<th>DOC (2L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (months)</td>
<td>5.24</td>
<td>6.90</td>
<td>8.80</td>
<td>7.06</td>
<td>8.45</td>
<td>6.51</td>
<td>9.40</td>
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<td>0.78</td>
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<td>0.35</td>
<td>0.30</td>
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BSC=best supportive care; GEM=gemcitabine; VNB=vinorelbine; PAX=paclitaxel; DOC=docetaxel; CDDP=cisplatin; LYS=life years saved; 2L=second line treatment.

*All costs obtained in or converted to 1999/2000 prices.58

*Cisplatin components not discounted; †dose in mg/m².
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, vinorelbine+cisplatin, 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.10 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, some 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,2 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,34 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.35

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 weighting should reflect the fact that patients value a short extension to a short life expectancy more than a short extension to a longer life expectancy.58 Further research is needed including good quality RCTs of different combinations of treatments among different subgroups of patients; use of these regimens alongside radiotherapy for suitable patients; adequate assessment of quality of life; development of methods for assessing the methodological quality of quality of life studies; comparison with non-drug treatments; and prospective economic analysis.

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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REFERENCES


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