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

A Clegg, D A Scott, P Hewitson, M Sidhu, N Waugh

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, docetaxel, 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 (SHPIC), 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 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 the summary 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, six gemcitabine, seven paclitaxel, and one did not describe randomisation. Five RCTs were judged to be of good quality (Jadad score 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, although for 18 this was difficult given the comparator (for example, BSC). Of the 33 RCTs, 15 stated that they were supported by or involved industry—two for docetaxel, four for gemcitabine, three for paclitaxel, and six for vinorelbine.

**Clinical effectiveness of docetaxel**

Of the three RCTs (table 1), two compared docetaxel with BSC as either first or second line treatment, while the other compared docetaxel with vinorelbine or ifosfamide as second line treatment. 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). 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. 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>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</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>
<td>None stated</td>
</tr>
<tr>
<td>Shepherd et al</td>
<td>Phase II, multicentre, randomised trial. ITT</td>
<td>Second line treatment: DOC 100 mg/m² (137 patients) every 3 weeks, BSC (70 patients)</td>
<td>Stage IIIB or IV NSCLC</td>
<td>Supported by Rhone-Poulenc Rorer</td>
</tr>
<tr>
<td>Roszkowski et al</td>
<td>Phase III, open-label, multicentre, randomised trial. ITT</td>
<td>DOC 100 mg/m² and BSC (100 patients)</td>
<td>NSCLC stage IIIB/IV</td>
<td>Supported by Rhone-Poulenc Rorer</td>
</tr>
<tr>
<td>Fossella et al</td>
<td>Phase III, open-label, multicentre, randomised trial. ITT</td>
<td>DOC 100 mg/m² (125 patients); DOC 75 mg/m² (125 patients); VNB or IFOS (123 patients)</td>
<td>Stage IIIB or IV NSCLC</td>
<td>None stated</td>
</tr>
<tr>
<td>Gmecitabine</td>
<td>Multicentre, randomised trial. ITT</td>
<td>GEM 1000 mg/m² with BSC (150 patients); BSC (150 patients)</td>
<td>Stage III (A or B) or IV NSCLC</td>
<td>Supported by Eli Lilly and Company</td>
</tr>
<tr>
<td>Anderson et al</td>
<td>Phase III, open label, multicentre, randomised trial. ITT</td>
<td>Gemcitabine 1000 mg/m² (137 patients); BSC (70 patients)</td>
<td>Stage III (A or B) or IV NSCLC</td>
<td>None stated</td>
</tr>
<tr>
<td>Roszkowski et al</td>
<td>Phase III, open-label, randomised trial. Partial ITT</td>
<td>DOC 100 mg/m² (27 patients); DOC 80 mg/m² (207 patients)</td>
<td>Stage III (A or B) or IV NSCLC</td>
<td>Supported by Eli Lilly and Company</td>
</tr>
<tr>
<td>Jadad quality score: 2/3</td>
<td>Phase III, open-label, randomised trial. ITT</td>
<td>GEM 1250 mg/m² (69 patients); VP-16 160 mg/m² (66 patients)</td>
<td>Stage III (A or B) or IV NSCLC</td>
<td>None stated</td>
</tr>
<tr>
<td>Jadad quality score: 2/5</td>
<td>Phase II, multicentre, open-label, randomised study. Not ITT</td>
<td>Docetaxel 100 mg/m² (21 patients); VNB 25 mg/m² with CDDP 80 mg/m² (200 patients); VNB 30 mg/m² (206 patients)</td>
<td>Stage III (A or B) or IV NSCLC</td>
<td>Supported by Eli Lilly and Company</td>
</tr>
<tr>
<td>Postmus et al</td>
<td>Phase II, multicentre, randomised trial. ITT</td>
<td>PAX 250 mg/m² with BSC (25 patients); MER 1000 mg/m² (35 patients); PIR 150 mg/m² (44 patients)</td>
<td>Stage IV NSCLC</td>
<td>None stated</td>
</tr>
<tr>
<td>Jadad quality score: 2/5</td>
<td>Phase II, multicentre, randomised trial. ITT</td>
<td>PAX 200 mg/m² with BSC (71 patients); BSC (78 patients)</td>
<td>Stage IV NSCLC</td>
<td>Supported by Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Fossella et al</td>
<td>Phase II, multicentre, randomised trial. ITT</td>
<td>CDDP 80 mg/m² with VM-26 100 mg/m² (38 patients); PAX 175 mg/m² and CDDP 80 mg/m² (207 patients)</td>
<td>Stage IV NSCLC</td>
<td>None stated</td>
</tr>
<tr>
<td>Jadad quality score: 2/5</td>
<td>Phase II, multicentre, randomised trial. ITT</td>
<td>CDDP 80 mg/m² with VM-26 100 mg/m² (166 patients); CDDP 100 mg/m² (166 patients)</td>
<td>Stage IV NSCLC</td>
<td>Supported by Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Jadad quality score: 2/5</td>
<td>Phase II, multicentre, randomised trial. ITT</td>
<td>CDDP 100 mg/m² with IFOS 3 mg/m² and VP-16 100 mg/m² (52 patients); CDDP 100 mg/m² (22 patients)</td>
<td>Stage IIIB or IV NSCLC</td>
<td>None stated</td>
</tr>
<tr>
<td>Jadad quality score: 2/5</td>
<td>Phase II, multicentre, randomised trial. ITT</td>
<td>CDDP 100 mg/m² with IFOS 3 mg/m² and VP-16 100 mg/m² (52 patients)</td>
<td>Stage IIIB or IV NSCLC</td>
<td>None stated</td>
</tr>
<tr>
<td>Jadad quality score: 2/5</td>
<td>Phase II, crossover, multicentre, randomised trial. ITT not stated</td>
<td>CDDP 100 mg/m² with IFOS 3 mg/m² and VP-16 100 mg/m² (52 patients)</td>
<td>Stage IIIB or IV NSCLC</td>
<td>Supported by Glaxo Wellcome</td>
</tr>
<tr>
<td>Jadad quality score: 2/5</td>
<td>Phase II, international, multicentre, randomised trial. ITT not stated</td>
<td>CDDP 100 mg/m² (119 patients); VNB 30 mg/m² (121 patients)</td>
<td>Stage IIIB or IV NSCLC</td>
<td>Supported by Pierre Fabre</td>
</tr>
<tr>
<td>Jadad quality score: 2/5</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 IIIB or IV NSCLC</td>
<td>Supported by Kyowa Hakka Company</td>
</tr>
<tr>
<td>Jadad quality score: 2/5</td>
<td>Phase II, international, multicentre, randomised trial. ITT not stated</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>
<td>None stated</td>
</tr>
<tr>
<td>Jadad quality score: 2/5</td>
<td>Phase II, multicentre, randomised trial. ITT</td>
<td>VNB 25 mg/m² (35 patients); VNB 25 mg/m² with CDDP 80 mg/m² (34 patients)</td>
<td>Stage IIIB or IV NSCLC</td>
<td>None stated</td>
</tr>
</tbody>
</table>
Paclitaxel, doxetaxel, gemcitabine, and vinorelbine in NSCLC

Two of the six RCTs assessing gemcitabine used cisplatin and etoposide as comparators, while the other four RCTs compared gemcitabine with BSC. Two of the six RCTs assessing gemcitabine used cisplatin, gemcitabine with etoposide, 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 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). 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.

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. 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. 

Clinical effectiveness of paclitaxel

Two of the six RCTs assessing gemcitabine used cisplatin and etoposide as comparators while the other four RCTs compared gemcitabine with BSC. Two of the six RCTs assessing gemcitabine used cisplatin, gemcitabine with etoposide, 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 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). 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.

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. 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.
<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 al45</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>Roszkowski et al38</td>
<td>Median survival: DOC arm=6.0 months (95% CI 5.0 to 8.0); BSC arm=7.7 months (95% CI 4.4 to 6.8) One year survival: DOC=25%; BSC=16%. Two year survival: DOC=12%; BSC=0%.</td>
</tr>
<tr>
<td>Fossella et al47</td>
<td>Median survival: DOC 100 mg/m2=5.5 months; VNB or IFOS=5.6 months. One year survival: DOC 100 mg/m2=21% (95% CI 14 to 28%); DOC 75 mg/m2=32% (95% CI 23 to 40%); VNB or IFOS=19% (95% CI 12 to 26%).</td>
</tr>
<tr>
<td><strong>Gemcitabine</strong></td>
<td></td>
</tr>
<tr>
<td>Anderson et al33</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). Estimated one year survival: GEM+BSC=25%; BSC=22%.</td>
</tr>
<tr>
<td>Bokkel Huinink et al39</td>
<td>Median survival: GEM=6.6 months (95% CI 4.9 to 7.3). One year survival: GEM=26%; CDDP+VP-16 arm=24% (p=NS).</td>
</tr>
<tr>
<td>Cardenal et al48</td>
<td>Estimated median survival: GEM arm=8.7 months (95% CI 7.7 to 10.2); VP-16 arm=7.2 months (95% CI 6.1 to 9.8) (p=0.02). One year survival probability: GEM=32%; VP-16=26% (p=NS).</td>
</tr>
<tr>
<td>Crino et al30</td>
<td>Overall median survival time: GEM+CDDP=8.6 months; TriComb=9.6 months (p=NS). One year survival: GEM +CDDP=33%; TriComb=34%.</td>
</tr>
<tr>
<td>Ferg et al43</td>
<td>One year survival: not reported.</td>
</tr>
<tr>
<td>Sandler et al44</td>
<td>Estimated median survival: GEM+CDDP=9.1 months (95% CI 8.3 to 10.6); CDDP=7.6 months (95% CI 6.5 to 8.2) (p=0.01). Estimated one year survival: GEM+CDDP=39%; DOC=CDDP=28%.</td>
</tr>
<tr>
<td><strong>Paclitaxel</strong></td>
<td></td>
</tr>
<tr>
<td>Bonomi et al32</td>
<td>Median survival: CDDP+VP-16=7.6 months; PAX (250 mg/m2)+CDDP=10 months; PAX (135 mg/m2)+CDDP=9.5 months. One year survival: CDDP+VP-16=31.8%; PAX (250 mg/m2)+CDDP=40.3%; PAX (135 mg/m2)+CDDP=37.4%.</td>
</tr>
<tr>
<td>Chang et al41</td>
<td>Median survival: PAX+VP-16=4.1 weeks; MER=19.9 weeks; PR=29.3 weeks (p&lt;NS). One year survival: PAX+VP=mean (SD) 4.1 (10.7%); MER=21.6% (p=NS).</td>
</tr>
<tr>
<td>Rana et al33</td>
<td>Median survival: PAX+CDDP=8.8 months (95% CI 5.7 to 10.2); BSC=4.8 months (95% CI 3.7 to 4.8). One year survival: PAX+CDDP=95%; BSC=41%; BSC=95% CI 18.39%. PAX+CDDP significantly associated with increased survival, hazard ratio 0.68 (95% CI 0.489 to 0.996; p=0.048).</td>
</tr>
<tr>
<td>Postmus et al32</td>
<td>Survival: Not assessed.</td>
</tr>
<tr>
<td>Gatzenberger et al31</td>
<td>Survival: PAX+CDDP=8.1 months (95% CI 7.3 to 9.2); CDDP=8.6 months (95% CI 7.1 to 10.3). Estimated one year survival: PAX+CDDP=30%; CDDP=36%.</td>
</tr>
<tr>
<td>Giaccone et al34</td>
<td>Median survival: CDDP+VM-26=9.9 months; PAX+CDDP=9.7 months (p=0.97). One year survival: CDDP+VM-26=41% (95% CI 33 to 49%); PAX+CDDP=43% (95% CI 25 to 51%) Two year survival: CDDP+VM-26=18% (95% CI 10 to 26%); PAX+CDDP=19% (95% CI 12 to 26%).</td>
</tr>
<tr>
<td>Baldini et al44</td>
<td>Median survival: CDDP+Mito+VDS=8.4 months; CDDP+IFOS+VNB=8.8 months; CBDCA+VNB=7.9 months. One year survival: CDDP+Mito+VDS=18%; CDDP+IFOS+VNB=15%; CBDCA+VNB=16%.</td>
</tr>
<tr>
<td>Colleoni et al46</td>
<td>Median survival: CDDP+Mito+VNB=9.9 months (range 3–14); CBDCA+VNB=8.8 months (range 1–18). One year survival: not assessed.</td>
</tr>
<tr>
<td>Colucci et al46</td>
<td>Median survival: CDDP+VNB+IFOS=9 months. IFOS+EPi (CDDP+VNB)=7 months (p=NS). One year survival: not assessed.</td>
</tr>
<tr>
<td>Comella et al47</td>
<td>Median survival: CDDP+VP-16=31 weeks; CBDCA+CDDP+VNB=27 weeks (p=NS). One year survival: CDDP+VP-16=25%; 5FU+LV=16% (p=0.06).</td>
</tr>
<tr>
<td>Crawford et al48</td>
<td>Median survival (estimated): VNB=30 weeks; 5FU+LV=22 weeks (p=0.03). One year survival: VNB=25%; 5FU+LV=16% (p=0.06).</td>
</tr>
<tr>
<td>Depierre et al37</td>
<td>Median survival: VNB=32 weeks; VNB+CDDP=33 weeks (p=NS). One year survival: not assessed.</td>
</tr>
<tr>
<td>Furuse et al50</td>
<td>Median survival: VNB arm=52.4 weeks; VDS arm=43.6 weeks (p=NS). One year survival: not assessed.</td>
</tr>
<tr>
<td>Le Chevalier et al49</td>
<td>Median survival: VNB+CDDP=40 weeks; VDS+CDDP=32 weeks (p&lt;0.09); VNB=31 weeks (p=0.05). One year survival: not assessed.</td>
</tr>
<tr>
<td>Loros et al51</td>
<td>Median survival: VNB=30 weeks; VNB+CDDP=38 weeks (p=NS). One year survival: not assessed.</td>
</tr>
<tr>
<td>Martoni et al36</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). One year survival: EPI+CDDP=42%; VNB+CDDP=39% (p=NS). Two year survival: EPI+CDDP=15%; VNB+CDDP=8% (p=NS).</td>
</tr>
<tr>
<td>Perol et al44</td>
<td>Median survival: CDDP+Mito+VDS=33.4 weeks; CDDP+Mito+VNB=34.3 weeks (p=NS). Overall two year survival: CDDP+Mito+VDS=15.6% (p=NS).</td>
</tr>
<tr>
<td>Wozniak et al46</td>
<td>Median survival: CDDP+VNB=8 months (p=0.01). One year survival: VNB+CDDP=36%; CDDP=20%. Two year survival: VNB+CDDP=12%; CDDP=6%. Median survival: VNB 28 weeks; BSC 21 weeks. 6 month survival: VNB=55%; BSC=41%.</td>
</tr>
<tr>
<td>Elderly Lung Cancer VNB Italian Study Group</td>
<td>One year survival: VNB=32%; BSC 14%.</td>
</tr>
<tr>
<td>Combined treatments</td>
<td></td>
</tr>
<tr>
<td>Comella et al45</td>
<td>Median survival: CDDP+Gem=50 weeks (95% CI 41 to 58); CDDP+Epi+VDS+ LON=33 weeks (95% CI 24 to 41). One year survival: CDDP+Gem=48%; CDDP+Epi+VDS=LON=29%. Two year survival: CDDP+Gem=19%; CDDP+Epi+VDS=LON=0%.</td>
</tr>
<tr>
<td>Comella et al38</td>
<td>Median survival: CDDP+Gem=51 weeks; CDDP+Gem=42 weeks; CDDP+VNB=35 weeks. One year survival: CDDP+Gem=45%; CDDP+Gem=40%; CDDP+Gem=34%.</td>
</tr>
<tr>
<td>Kozimski et al52</td>
<td>Median survival: CDDP+Gem=50 weeks (95% CI 41 to 58); CDDP+Epi+VDS=7.4 months (95% CI 5.3 to 13.3). One year survival: estimated: PAX+IFOS=35% (95% CI 24; 52%); VNB+IFOS=38% (95% CI 26 to 55%).</td>
</tr>
<tr>
<td>Frasci et al58</td>
<td>Median survival: GEM+VNB=29 wks; VNB=18 weeks. Six month survival: GEM+VNB=56%, VNB=32%. One year survival: estimated: GEM+VNB=30%; VNB=13%.</td>
</tr>
</tbody>
</table>

GEM=gemcitabine; IFOS=ifosfamide; ITT=intention to treat; DOC=docetaxel; PAX=paclitaxel; 5FU=5-fluouracil; Mito=mitomycin; VDS=vinorelbine; VM-26=teniposide; VNB=vinorelbine; VP-16=etoposide; 5 FU=fluorouracil.  

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; N盐城=non-small cell lung cancer; PAX=paclitaxel; PIR=pipexantrone; VDS=vinorelbine; 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 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, only five patients stopped treatment because of severe toxic events in the comparison of vinorelbine with BSC.49

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 or cisplatin and gemcitabine and cisplatin and vinorelbine (table 1).46 Other RCTs compared paclitaxel and ifosfamide with vinorelbine and ifosfamide,47 gemcitabine and vinorelbine with vinorelbine,46 and paclitaxel and carboplatin with paclitaxel and gemcitabine.48 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).46 Assessment of the effects on quality of life was limited, with none of the combined treatments affecting quality of life (table 3).47–51 Adverse effects varied with the components of the combined treatments, although no significant differences were evident.47–51

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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 difficulties associated with blinding many of the treatments.
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 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. How often 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 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. 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.

ACKNOWLEDGEMENT

We thank the advisory group for advice and peer review of a draft of the original report for NICE, including: Dr J Baird, Director of Patient Care, Roy Castle Lung Cancer Foundation; Dr Frances Bowen, Consultant in Respiratory and General Medicine, Hammersmith Hospital, London; Dr Doug Coyle, Principal Investigator, Health Economics, Clinical Epidemiology Unit, The Ottawa Hospital, Ottawa, Canada; Dr Michael Cullen, Consultant and Hon Reader in Medical Oncology, Cancer Centre at the Queen Elizabeth Hospital, Birmingham; Dr Anna Gregor, Consultant in Clinical Oncology, Western General Hospital, Edinburgh; Dr P Hopwood, Hon Consultant Psychiatrist, CRC Psychological Medicine Group, Christie Hospital, Manchester; Dr Fergus MacBeth, Chairman of COIN Lung Cancer Group/Member of the Cochrane Lung Cancer Group, Consultant Oncologist, St Helen’s Hospi-

cal, Cardiff; Ms Kirsten Major, Health Economist, Ayr and Arran Health Board; Dr Ben Marshall, Consultant in Respiratory Medicine, Southampton General Hospital; Dr Martin Muers, Consultant in Respiratory Medicine, Leeds; Professor J E Smith, Professor of Cancer Medicine, The Royal Marsden Hospital; Professor A Sutton, Professor N Thatchers, Professor of Oncology, CRC Department of Medical Oncology, Christie CRC Research Centre, Christie Hospital, Manchester. We would also like to thank Dr Pam Royle and Ms Liz Hudson for their support with obtaining information; the South East Scotland Lung Study Group; SHPIC Costing Unit; and Dr Winter and colleagues at Kings Cross Hospital in Dundee.

Authors’ affiliations

A Clegg, D A Scott, P Hewitson, M Sidhu, N Waugh, Southampton Health Technology Assessments Centre, Wessex Institute for Health Research and Development, University of Southampton, Southampton SO16 7PX, UK

Conflits of interest: none

Funding/support: This study was supported by the NHS R&D HTA programme. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NHS Executive.

REFERENCES


Clinical and cost effectiveness of paclitaxel, docetaxel, gemcitabine, and vinorelbine in non-small cell lung cancer: a systematic review
A Clegg, D A Scott, P Hewitson, M Sidhu and N Waugh

Thorax 2002 57: 20-28
doi: 10.1136/thorax.57.1.20

Updated information and services can be found at:
http://thorax.bmj.com/content/57/1/20

These include:

References
This article cites 52 articles, 25 of which you can access for free at:
http://thorax.bmj.com/content/57/1/20#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Chemotherapy (183)
Health policy (183)
Health service research (169)
Lung cancer (oncology) (670)
Lung cancer (respiratory medicine) (670)
Lung neoplasms (608)
Clinical trials (epidemiology) (557)
Internet (104)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/