ORIGINAL ARTICLE

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.[1] Survival rates vary within England and Wales and across Europe.[2]

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,[3] but recent developments have led to cautious optimism as a result of improvements in symptom relief, quality of life, and survival.[4–9] 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.[10] 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.[11]

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.[12]

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).[12] 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.[13]

The quality of the RCTs was assessed using the Jadad scale.[14] 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.[12] 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.[12] 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 m^2. 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.[12] 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.[12] 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*[15] and non-patient based utility estimates were also examined.[15 16] 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,[14 17–19] six gemcitabine,[13 20–27] six paclitaxel,[28–33] 13 vinorelbine,[34–46] and five combined treatments.[47–51] 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 28 29 32 33 35 42–44 46 47 49–51] 32 had inadequate descriptions of blinding,[13 17–24 28–47 49–51] although for 18 this was difficult given the comparator (for example, BSC),[13 18–24 31 33 43–47 49–51] and one did not describe withdrawals.[24] Of the 33 RCTs, 15 stated that they were supported by or involved industry—two for docetaxel,[17 18] four for gemcitabine,[13 20 21 24–26] three for paclitaxel,[30 31 33] and six for vinorelbine.[38–41 44 46]

Clinical effectiveness of docetaxel

Of the three RCTs (table 1), two compared docetaxel with BSC as either first[18] 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/m^2 was used as second line treatment, improving median survival by nearly 3 months (docetaxel 75 mg/m^2 7.5 months *v* BSC 4.6 months, p=0.01).[19] One year survival rates were significantly higher for patients given docetaxel 75 mg/m^2 (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).[18 19] 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).[18] When used as second line treatment, docetaxel had a significant beneficial effect on pain (p<0.01).[19] 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

Study details	Design	Intervention	Subjects	Conflicts of interest
Docetaxel				
Shepherd *et al*[19] Jadad quality score: 2/3	Phase II, multicentre, randomised trial. ITT	Second line treatment: DOC 100 mg/m^2 (49 patients), DOC 75 mg/m^2 (55 patients), and BSC (100 patients)	Stage IIIA/B or IV NSCLC	None stated
Roszkowski *et al*[18] Jadad quality score: 2/3	Phase III, open-label, multicentre, randomised trial. ITT	First line treatment: DOC 100 mg/m^2 (137 patients) every 3 weeks, BSC (70 patients)	Stage IIIB or IV NSCLC	Supported by Rhone-Poulenc Rorer
Fossella *et al*[17] Jadad quality score: 2/5	Phase III, open label, multicentre, randomised trial. ITT	Second line treatment: DOC 100 mg/m^2 (125 patients); DOC 75 mg/m^2 (125 patients); VNB or IFOS (123 patients)	NSCLC stage IIIB/IV	Supported by Rhone-Poulenc Rorer
Gemcitabine				
Anderson *et al*[13] Jadad quality score: 3/3	Multicentre, randomised trial. ITT	GEM 1000 mg/m^2 with BSC (150 patients); BSC (150 patients)	Symptomatic locally advanced or metastatic NSCLC	Supported by Eli Lilly and Company
Bokkel Huinink *et al*[20 57] Jadad quality score: 2/5	Phase II, multicentre, open-label, randomised study. Not ITT	GEM 1000 mg/m^2 (72 patients); CDDP 100 mg/m^2 with VP-16 100 mg/m^2 (75 patients)	Stage IIIA (inoperable), IIIB or IV NSCLC	Supported by Eli Lilly and Company
Cardenal *et al*[21] Jadad quality score: 2/5	Phase III, multicentre, randomised trial. ITT	GEM 1250 mg/m^2 (69 patients); VP-16 100 mg/m^2 (66 patients)	Stage IIIB or IV NSCLC	Supported by Eli Lilly and Company
Crino *et al*[22] Jadad quality score: 2/5	Phase III, multicentre, randomised trial. Partial ITT	GEM 1000 mg/m^2 with CDDP 100 mg/m^2 (155 patients); MITO 6 mg/m^2, IFOS 3000 mg/m^2, with CDDP 100 mg/m^2 (TriComb) (152 patients)	Stage IIIB or IV NSCLC	None stated
Perng *et al*[23] Jadad quality score: 3/5	Phase II, randomised trial. ITT	GEM 1250 mg/m^2 (27 patients); CDDP 80 mg/m^2 with VP-16 80 mg/m^2 (26 patients)	Stage III (A or B) or IV NSCLC	None stated
Sandler *et al*[24] Jadad quality score: 1/5	Phase III, multicentre, randomised trial. ITT	GEM 1000 mg/m^2 with CDDP 100 mg/m^2 (260 patients); CDDP 100 mg/m^2 (262 patients)	Stage IIIA or IIIB or IV NSCLC	Supported by Eli Lilly
Paclitaxel				
Bonomi *et al*[28] Jadad quality score: 2/5	Phase III, multicentre, randomised trial. Not ITT	VP-16 100 mg/m^2 with CDDP 75 mg/m^2 (193 patients); PAX 250 mg/m^2 with CDDP 75 mg/m^2 (191 patients); PAX 135 mg/m^2 with CDDP 75 mg/m^2 (190 patients)	Stage IIIB or IV NSCLC	None stated
Chang *et al*[29] Jadad quality score: 2/5	Phase II, randomised study. Not ITT	PAX 250 mg/m^2 (25 patients); MER 1000 mg/m^2 (35 patients); PIR 150 mg/m^2 (44 patients)	Stage IV NSCLC	None stated
Ranson *et al*[33] Jadad quality score: 2/3	Phase III, multicentre, randomised trial. ITT not stated	PAX 200 mg/m^2 with BSC (79 patients); BSC (78 patients)	Stage IIIB or IV NSCLC	Supported by Bristol-Myers Squibb
Postmus *et al*[32] Jadad quality score: 2/5	Phase II, multicentre, randomised trial. Interim analysis. ITT not stated	CDDP 80 mg/m^2 with VM-26 100 mg/m^2 (38 patients); PAX 175 mg/m^2 and CDDP 80 mg/m^2 (35 patients)	Stage IIIB or IV NSCLC	None stated
Gatzemier *et al*[30] Jadad quality score: 2/5	Phase III, multicentre randomised trial. ITT	PAX 175 mg/m^2 with CDDP 80 mg/m^2 (207 patients); CDDP 100 mg/m^2 (207 patients)	Stage IIIB or IV NSCLC	Supported by Bristol-Myers Squibb
Giaccone *et al*[31] Jadad quality score: 3/5	Phase III, randomised trial. ITT	CDDP 80 mg/m^2 with VM-26 100 mg/m^2 (166 patients); PAX 175 mg/m^2 with CDDP 80 mg/m^2 (166 patients)	Locally advanced or metastatic NSCLC	Supported by Bristol-Myers Squibb
Vinorelbine				
Baldini *et al*[34] Jadad quality score: 3/5	Phase II, multicentre, randomised study. ITT	CDDP 80 mg/m^2 with VDS 3 mg/m^2 and MITO 6 mg/m^2 (49 patients); CDDP 80 mg/m^2 with IFOS 3 mg/m^2 with VNB 25 mg/m^2 (48 patients); CBDCA 350 mg/m^2 with VNB 25 mg/m^2 (43 patients)	Stage IIIB or IV NSCLC	None stated
Colleoni *et al*[35] Jadad quality score: 1/5	Phase II, randomised trial. ITT not stated	CDDP 100 mg/m^2 with MITO 8 mg/m^2 and VNB 25 mg/m^2 (26 patients); CBDCA 400 mg/m^2 with VNB 25 mg/m^2 (26 patients)	Stage IIIB and IV NSCLC	None stated
Colucci *et al*[36] Jadad quality score: 3/5	Phase III, multicentre, randomised study. ITT	Two step treatment arms – CDDP 100 mg/m^2 with VNB 25 mg/m^2, followed by IFOS 2.5 g/m^2 and EPI 100 mg/m^2 (53 patients). IFOS 2.5 g/m^2 and EPI 100 mg/m^2 , followed by CDDP 100 mg/m^2 and VNB 25 mg/m^2 (47 patients)	Stage IIIA/B and IV NSCLC	None stated
Comella *et al*[37] Jadad quality score: 3/5	Phase III, multicentre, randomised trial. ITT	CDDP 40 mg/m^2 with VP-16 100 mg/m^2 (53 patients). CBDCA 250 mg/m^2 with CDDP 30 mg/m^2, VP-16 100 mg/m^2 and VNB 30 mg/m^2 (52 patients)	Stage IIIB or IV NSCLC	None stated
Crawford *et al*[38] Jadad quality score: 3/5	Phase II, multicentre, randomised trial. ITT	VNB 30 mg/m^2 (143 patients). 5-FU 425 mg/m^2 with LV 20 mg/m^2 (68 patients)	Stage IV NSCLC	Supported by Glaxo Wellcome
Depierre *et al*[39] Jadad quality score: 3/5	Phase III, multicentre, randomised trial. ITT	VNB 30 mg/m^2 (119 patients). VNB 30 mg/m^2 with CDDP 80 mg/m^2 (121 patients)	Stage IIIA/B or IV NSCLC	Supported by Pierre Fabre
Furuse *et al*[40] Jadad quality score: 3/5	Phase II, crossover, multicentre, randomised trial. ITT not stated	(VNB arm) VNB 25 mg/m^2 (103 patients) with non-responders switching to VDS 3 mg/m^2+CDDP 80 mg/m^2; (VDS arm) VDS 3 mg/m^2 (101 patients) with non-responders switching to VNB 20 mg/m^2+CDDP 80 mg/m^2	Stage IIIB or IV NSCLC	Supported by Kyowa Hakka Company
Le Chevalier *et al*[41] Jadad quality score: 3/5	Phase II, international, multicentre, randomised trial. ITT not stated	VNB 30 mg/m^2 with CDDP 120 mg/m^2 (206 patients); VDS 3 mg/m^2 with CDDP 120 mg/m^2 (200 patients); VNB 30 mg/m^2 (206 patients)	Stage III or IV NSCLC	Supported by Pierre Fabre
Lorusso *et al*[42] Jadad quality score: 2/5	Phase III, multicentre, randomised trial. Not ITT	VNB 25 mg/m^2 (35 patients); VNB 25 mg/m^2 with CDDP 80 mg/m^2 (34 patients)	Inoperable NSCLC	None stated

Table 1 Continued

Study details	Design	Intervention	Subjects	Conflicts of interest
Martoni *et al*[43] Jadad quality score: 2/5	Phase II, multicentre, randomised trial. ITT	EPI 120 mg/m^2 with CDDP 60 mg/m^2 (102 patients); VNB 25 mg/m^2 with CDDP 60 mg/m^2 (110 patients)	Locally advanced or metastatic NSCLC	None stated
Perol *et al*[44] Jadad quality score: 2/5	Phase II, open, multicentre, randomised trial. Partial ITT analysis	CDDP 120 mg/m^2 with MITO 8 mg/m^2 and VDS 3 mg/m^2 (113 patients). CDDP 120 mg/m^2 with MITO 8 mg/m^2 and VNB 25 mg/m^2 (114 patients)	Stage III or IV NSCLC	Supported by Pierre Fabre
Wozniak *et al*[46] Jadad quality score: 2/5	Phase III, multicentre, randomised trial. Partial ITT analysis	VNB 25 mg/m^2 with CDDP 100 mg/m^2 (206 patients). CDDP 100 mg/m^2 (209 patients)	Stage IIIB or IV NSCLC	Supported by Glaxo Wellcome
ELVIS[45] Jadad quality score: 3/3	Phase III, multicentre, randomised trial. Not ITT	VNB 30 mg/m^2 (76 patients); BSC (78 patients)	Stage IIIB or IV	None stated
Combined treatments				
Comella *et al*[47] Jadad quality score: 2/5	Phase II, randomised trial. ITT	CDDP 50 mg/m^2 with GEM 100 mg/m^2 and VNB 25 mg/m^2 (57 patients). CDDP 80 mg/m^2 with EPI 80 mg/m^2 and VDS 3 mg/m^2 and LON 150 mg/m^2 (54 patients)	Stage IIIB or IV NSCLC	None stated
Comella *et al*[48] Jadad quality score: 3/5	Phase III, randomised trial. Interim analysis. ITT	CDDP 50 mg/m^2 with GEM 1000 mg/m^2 and VNB 25 mg/m^2 (60 patients). CDDP 100 mg/m^2 with GEM 1000 mg/m^2(60 patients). CDDP 120 mg/m^2 with VNB 30 mg/m^2 (60 patients)	Stage IIIB or IV NSCLC	None stated
Kosmidis *et al*[50] Jadad quality score: 2/5	Phase III, randomised trial. Preliminary results. ITT not stated	PAX 200 mg/m^2 with CBDCA (63 patients). PAX 200 mg/m^2 with GEM 1000 mg/m^2 (64 patients)	Stage IIIA (inoperable), stage IIIB or IV NSCLC	Supported by Eli Lilly and Company
Perry *et al*[51] Jadad quality score: 2/5	Phase II, randomised trial. ITT not stated	PAX 250 mg/m^2 with IFOS 1.6 g/m^2 (48 patients). VNB 30 mg/m^2 with IFOS 1.6 g/m^2 (45 patients)	Stage IIIB or IV NSCLC	None stated
Frasci *et al*[49] Jadad quality score: 2/5	Phase III, randomised trial. Interim analysis. ITT	GEM 1200 mg/m^2 with VNB 30 mg/m^2 (60 patients). VNB 30 mg/m^2 (60 patients)	Stage IIIB or IV NSCLC	None stated

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; PIR=piroxantrone; VDS=vindesine; VM-26=teniposide; VNB=vinorelbine; VP16=etoposide; 5-FU=fluorouracil.

receiving 100 mg/m^2 docetaxel, necessitating a reduction in dose to 75 mg/m^2.[19]

Clinical effectiveness of gemcitabine

Two of the six RCTs assessing gemcitabine used cisplatin and etoposide as comparators[20 23] while the other four RCTs compared gemcitabine and BSC with BSC alone,[13] gemcitabine with etoposide,[21] gemcitabine and cisplatin with cisplatin,[24] and gemcitabine and cisplatin with mitomycin, ifosfamide and cisplatin (table 1).[22] 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; $p<0.05$)[21] 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).[24] 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%, $p<0.005$).[13] 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 ($p<0.001$)[22] or etoposide (significance not stated)[21] 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,[29] as well as in several combinations including paclitaxel and cisplatin compared with etoposide with cisplatin,[28] paclitaxel and BSC with BSC,[33] paclitaxel and cisplatin with teniposide and cisplatin,[31 32] paclitaxel and cisplatin against cisplatin.[30] 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).[33] One and two year survival was improved for patients receiving paclitaxel,[28 29 31 33] although only the comparison between paclitaxel and BSC (95% CI 20 to 41) with BSC (95% CI 18 to 39) was statistically significant.[33] 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 ($p<0.05$)[33] and for paclitaxel and cisplatin compared with teniposide and cisplatin (fatigue $p<0.01$, appetite loss $p<0.001$).[31] Adverse events, whether haematological or non-haematological, differed depending on the interventions compared. Three RCTs assessing paclitaxel with merbarone and piroxantrone,[29] paclitaxel and cisplatin with cisplatin alone,[30] and paclitaxel and BSC with BSC only[33] 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.[31 32] Adverse effects associated with paclitaxel included thrombocytopenia, leukopenia, 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.[34 35 39 41 42] Two RCTs used a form of crossover design,[36 40] although patients in one RCT only changed interventions when considered non-responders.[40] 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

Study details	Patient survival
Docetaxel	
Shepherd *et al*[19]	*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/m^2)=5.9 months (p=0.78); DOC (75 mg/m^2)=7.5 months (p=0.01). *One year survival:* BSC=19%; DOC (both doses)=29%; DOC (100 mg/m^2)=19%; DOC (75 mg/m^2)=37%; BSC=12%.
Roszkowski *et al*[18]	*Median survival:* DOC arm=6.0 months (95% CI 5.0 to 8.0); BSC arm=5.7 months (95% CI 4.4 to 6.8) *One year survival:* DOC=25%; BSC=16%. *Two year survival:* DOC=12%; BSC=0%
Fossella *et al*[17]	*Median survival:* DOC 100 mg/m^2 =5.5 months; 75 mg/m^2 =5.7 months; VNB or IFOS=5.6 months. *One year survival:* DOC 100 mg/m^2 =21% (95% CI 14 to 28%); DOC 75 mg/m^2=32% (95% CI 23 to 40%); VNB or IFOS=19% (95% CI 12 to 26%).
Gemcitabine	
Anderson *et al*[13]	*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% *Estimated two year survival:* GEM+BSC=6%; BSC=7%.
Bokkel Huinink *et al*[20 57]	*Median survival:* GEM=6.6 months (95% CI 4.9 to 7.3) CDDP+VP-16 arm=7.6 months (95% CI 5.4 to 9.3) *One year survival:* GEM=26%; CDDP+VP-16 arm=24% (p=NS)
Cardenal *et al*[21]	*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).
Crino *et al*[22]	*Overall median survival time:* GEM+CDDP=8.6 months; TriComb=9.6 months (p=NS). *One year survival:* GEM +CDDP=33%; TriComb=34%.
Perng *et al*[23]	*Median survival duration:* GEM=37 weeks; CDDP+VP-16=48 weeks (p=NS). *One year survival:* not reported.
Sandler *et al*[24]	*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%; CDDP=28%
Paclitaxel	
Bonomi *et al*[28]	*Median survival:* CDDP+VP-16=7.6 months; PAX (250 mg/m^2)+CDDP=10 months; PAX (135 mg/m^2)+CDDP=9.5 months *One year survival:* CDDP+VP-16=31.8%; PAX (250 mg/m^2)+ CDDP=40.3%; PAX (135 mg/m^2)+CDDP=37.4%.
Chang *et al*[29]	*Median survival:* PAX=24.1 weeks; MER=19.9 weeks; PIR=29.3 weeks (p=NS). *One year survival:* PAX=mean (SD) 41.7 (10)%; MER=21.6 (7)%; PIR=22.6 (7)% (p=NS).
Ranson *et al*[33]	*Median survival:* PAX+BSC=6.8 months (95% CI 5.7 to 10.2); BSC=4.8 months (95% CI 3.7 to 6.8). *One year survival:* PAX+BSC=95% CI: 20; 41%, BSC=95% CI: 18; 39%. PAX+BSC significantly associated with increased survival, hazard ratio 0.68 (95% CI 0.489 to 0.996; p=0.048)
Postmus *et al*[32]	*Survival:* Not assessed.
Gatzemier *et al*[30]	*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%.
Giaccone *et al*[31]	*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%).
Vinorelbine	
Baldini *et al*[34]	*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%.
Colleoni *et al*[35]	*Median survival:* CDDP+MITO+VNB=9.9 months (range 3–14); CBDCA+VNB=8.8 months (range 1–18). *One year survival:* not assessed.
Colucci *et al*[36]	*Median survival:* CDDP+VNB (IFOS+EPI)=9 months. IFOS+EPI (CDDP+VNB)=7 months (p=NS). *One year survival:* not assessed.
Comella *et al*[37]	*Median survival:* CDDP+VP-16=31 weeks; CBDCA+CDDP+ VNB=27 weeks (p=NS).
Crawford *et al*[38]	*Median survival (estimated):* VNB=30 weeks; 5-FU+LV=22 weeks (p=0.03). *One year survival:* VNB=25%; 5-FU+LV=16% (p=0.06).
Depierre *et al*[39]	*Median survival:* VNB=32 weeks; VNB+CDDP=33 weeks (p=NS). *One year survival:* not assessed.
Furuse *et al*[40]	*Median survival:* VNB arm=52.4 weeks; VDS arm=43.6 weeks (p=NS). *One year survival:* not assessed.
Le Chevalier *et al*[41]	*Median survival:* VNB+CDDP=40 weeks; VDS+CDDP=32 weeks (p<0.09); VNB=31 weeks (p<0.05). *One year survival:* not assessed.
Lorusso *et al*[42]	*Median survival:* VNB=30 weeks; VNB+CDDP=38 weeks (p=NS). *One year survival:* not assessed.
Martoni *et al*[43]	*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).
Perol *et al*[44]	*Median survival:* CDDP+MITO+VDS=33.4 weeks; CDDP+MITO+VNB=34.5 weeks (p=NS). *Overall two year survival:* CDDP+MITO+VDS=15.6%; CDDP+MITO+VNB=9%, (p=NS).
Wozniak *et al*[46]	*Median survival:* VNB+CDDP=8 months, CDDP=6 months (p<0.01). *One year survival:* VNB+CDDP=36%; CDDP=20%. *Two year survival:* VNB+CDDP=12%; CDDP=6%.
Elderly Lung Cancer VNB Italian Study Group[45]	*Median survival:* VNB 28 weeks; BSC 21 weeks. *6 month survival:* VNB 55%; BSC 41%. *One year survival:* VNB 32%; BSC 14%.
Combined treatments	
Comella *et al*[47]	*Median survival:* CDDP+GEM+VNB=50 weeks (95% CI 41 to 58); CDDP+EPI+VDS+ LON=33 weeks (95% CI 24 to 41) *One year survival:* CDDP+GEM+VNB=48%; CDDP+EPI+VDS+ LON=29% *Two year survival:* CDDP+GEM+VNB=19%, CDDP+EPI+VDS+ LON=0%.
Comella *et al*[48]	*Median survival:* CDDP+GEM+VNB=51 weeks; CDDP+GEM=42 weeks; CDDP+VNB=35 weeks *One year survival:* CDDP+GEM+VNB=45%; CDDP+GEM=40%; CDDP+VNB=34%
Kosmidis *et al*[50]	*Median survival:* not assessed. *One year survival:* not assessed.
Perry *et al*[51]	*Median survival:* PAX+IFOS=8.5 months; VNB+IFOS=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%).
Frasci *et al*[49]	*Median survival:* GEM+VNB=29 wks; VNB=18 weeks. *Six month survival (estimated):* GEM+VNB=56%; VNB=32%. *One year survival (estimated):* GEM+VNB=30%; VNB=13%.

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; PIR=piroxantrone; VDS=vindesine; VM-26=teniposide; VNB=vinorelbine; VP-16=etoposide; 5-FU=fluorouracil.

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

Study details	Quality of life
Docetaxel	
Shepherd *et al*[19]	QoL parameters favoured DOC patients, significant differences for pain (p=0.006), fatigue (p=0.06) and tumour related medications used (p=0.02).
Roszkowski *et al*[18]	DOC had significantly favourable effects on emotional functioning (p<0.05), nausea/vomiting (p=0.04), pain (p<0.0001) and dyspnea (p=0.02). No difference between global health status and physical functioning scores (p=NS).
Gemcitabine	
Anderson *et al*[13]	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)
Bokkel Huinink *et al*[20 57]	No significant difference in change from baseline on global, physical, role, cognitive, emotional and social aspects of QoL (p>0.05).
Cardenal *et al*[21]	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.
Crino *et al*[22]	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).
Sandler *et al*[24]	No significant differences in QoL between treatment arms in change from baseline.
Paclitaxel	
Bonomi *et al*[28]	No significant difference between treatment arms in change from baseline.
Ranson *et al*[33]	No statistically significant difference between arms in change from baseline.
Gatzemier *et al*[30]	On symptom scales CDDP patients had significant worsening of nausea and vomiting (p<0.0003), appetite loss (p<0.02) and constipation (p<0.032), while PAX+CDDP patients had significant worsening of hair loss and peripheral neuropathy (p<0.0001).
Giaccone *et al*[31]	Patients on PAX+CDDP had significant beneficial effects on functional scales and some symptom scales at 6 weeks (fatigue (p=0.006) and appetite loss (p<0.001)), which disappeared at 12 weeks.
Vinorelbine	
Crawford *et al*[38]	No significant difference between treatment arms in change from baseline (no data presented).
Martoni *et al*[43]	No significant difference in change from baseline between treatment arms.
ELVIS[45]	On EORTC functional and symptom scales and on LC-13, 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).
Combined treatments	
Comella *et al*[47]	Improved QoL score CDDP+GEM+VNB=59%, CDDP+EPI+VDS+ LON=39% (p not stated)
Frasci *et al*[49]	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).

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 (LQ-C30 and LC13 scales); TriComb=combination of MITO, IFOS and CDDP; VDS=vindesine; VNB=vinorelbine; VP-16=etoposide.

including vinorelbine alone; vinorelbine and cisplatin; vinorelbine and carboplatin; vinorelbine, carboplatin and cisplatin; vinorelbine, mitomycin and cisplatin; vinorelbine, cisplatin and ifosfamide; vinorelbine, cisplatin, ifosfamide and epirubicin; and vinorelbine, cisplatin, carboplatin and etoposide. One RCT concentrated on elderly patients aged over 70 years.[45] Of the 11 RCTs showing improvement in median survival for patients receiving vinorelbine in differing combinations,[34–36 38–42 44–46] the comparisons of vinorelbine with fluorouracil and leucovorin (30 weeks *v* 22 weeks, p<0.05) and vinorelbine and cisplatin with cisplatin (8 months *v* 6 months, p<0.005) showed statistically significant increases in survival (table 2).[38 46] Patient survival to 1 and 2 years was assessed in six RCTs with none showing a significant difference between the combinations of interventions.[34 38 43–46] The effect of vinorelbine on quality of life was assessed in three RCTs (table 3),[38 43 45] although only the comparison between vinorelbine and BSC showed any statistically significant difference.[45] Patients receiving vinorelbine experienced significant improvements in cognitive function (p<0.05), dyspnoea (p=0.05), and pain medication (p=0.01), but significant worsening 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.[43 44] 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).[43] 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.[44] In addition, five patients stopped treatment because of severe toxic events in the comparison of vinorelbine with BSC.[45]

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[47] or cisplatin and gemcitabine and cisplatin and vinorelbine (table 1).[48] Other RCTs compared paclitaxel and ifosfamide with vinorelbine and ifosfamide,[51] gemcitabine and vinorelbine with vinorelbine,[49] and paclitaxel and carboplatin with paclitaxel and gemcitabine.[50] 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).[47] Assessment of the effects on quality of life was limited, with none of the combined treatments affecting quality of life (table 3).[47–49 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.

Table 4 Cost effectiveness results†

	BSC	GEM	GEM+ CDDP	VNB	VNB+ CDDP	PAX	PAX (135)* +CDDP	PAX (175)* +CDDP	PAX (250)* +CDDP	DOC	DOC (2L)
Median no of cycles		3	4	3	3	5	5	5	4	3	3
No. of administrations (GEM, VNB, etc)		9	12	12	12	5	5	5	4	3	3
No. of CDDP administrations		0	4	0	3	0	5	5	4	0	0
Drug cost (GEM,VNB, etc) (£)		2637	3516	2140	2140	6858	4364	5610	6483	3975	3300
Drug cost (CDDP) (£)			243		219		243	243	204		
Administration/side effects/chem counselling (£)		1495	2562	1823	2377	1435	1696	1696	1460	1065	1065
Average cost per patient (£)	3342	4132	6321	3963	4736	8293	6304	7550	8147	5040	4365
Incremental cost (*v* BSC) (£)		789	2979	620	1394	4951	2962	4208	4804	1698	1023
Median survival (months)	5.24	6.90	8.80	7.06	8.45	6.51	9.40	8.81	10.00	6.00	5.94
Life years saved (LYS)	0.44	0.58	0.73	0.59	0.70	0.54	0.78	0.73	0.83	0.50	0.49
Average cost per LYS (£)	7658	7184	8623	6738	6726	15283	8048	10281	9776	10081	8824
Incremental median survival (months) (*v* BSC)		1.66	3.56	1.82	3.21	1.27	4.16	3.58	4.76	0.76	0.70
Incremental LYS (*v* BSC)		0.14	0.30	0.15	0.27	0.11	0.35	0.30	0.40	0.06	0.06
Incremental cost per LYS (*v* BSC) (£)		5690	10041	4091	5206	46610	8537	14124	12104	26707	17546

BSC=best supportive care; GEM=gemcitabine; VNB=vinorelbine; PAX=paclitaxel; DOC=docetaxel; CDDP=cisplatin; LYS=life years saved; 2L=second line treatment.
*Dose in mg/m^2. †All costs obtained in or converted to 1999/2000 prices.[58]

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

	GEM	GEM+ CDDP	VNB	VNB+ CDDP	PAX	PAX (135)† +CDDP	PAX (175)† +CDDP	PAX (250)† +CDDP	DOC	DOC (2L)
Baseline	5690	10041	4091	5206	46610	8537	14124	12104	26707	17546
3 cycles: VNB,GEM,DOC; 4 PAX	5690	5145	4091	5206	31957	5198	9398	12104	26707	17546
60% prob. half course, 40% full course	D	2478	D	2808	16461	2179	4879	7204	7952	569
VNB cycle: 21 days/3 administrations	NA	NA	D	1982	NA	NA	NA	NA	NA	NA
VNB cycle: 21 days/2 administrations	NA	NA	D	D	NA	NA	NA	NA	NA	NA
25% discount on BNF	939	7079	564	3208	30469	5392	9416	8021	11078	3398
50% discount on BNF	D	4116	D	1209	14327	2248	4708	3937	D	D
Anti-emetics £150	6771	10547	5080	5767	48023	8970	14627	12482	29066	20119
Bethelot's mean survival[15]	1925	NA	2216	3167	NA	5196	NA	8429	NA	NA
Berthelot's QoL utilities[15]	5538	NA	5105	7290	NA	11296	NA	16358	NA	NA
Best survival	2903	9253	3442	3833	38008	NA	11314	NA	7375	5425
Worst survival	20458	12484	5895	11430	163647	NA	17636	NA	X	46680
SESLS BSC cost (£3572)	4034	9267	2576	4348	44447	7875	13352	11525	23093	13605
Lower BSC estimate (£2200)	13923	13892	11622	9473	57364	11830	17957	14982	44670	37134
Best cycles	D	NA	NA	NA	NA	NA	NA	NA	NA	NA
Worst cycles	23089	14938	11677	10467	NA	NA	18849	NA	NA	NA
OP administration	NA	8255	NA	3722	43058	NA	NA	NA	23146	13664
Reduced dose (if <20% of vial used)	NA	NA	1618	3805	NA	NA	NA	NA	NA	NA

BSC=best supportive care; GEM=gemcitabine; VNB=vinorelbine; PAX=paclitaxel; DOC=docetaxel; CDDP=cisplatin; LYS=life years saved; 2L=second line treatment; SESLS=South-east Scotland Lung Study; D=dominant strategy *v* BSC. It is not appropriate to show a figure when a strategy is dominant; X=dominated, higher cost and lower survival than BSC.
Data in italics were provided by industry.
*Cisplatin components not discounted; †dose in mg/m^2.

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

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*[52] 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, one 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,[53] 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,[54] 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.[55]

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.[56] 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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