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

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The technologies assessed were:

- gemcitabine (GEM),
- GEM plus cisplatin (CDDP),
- vinorelbine (VIN),
- VIN plus CDDP,
- paclitaxel (PAX),
- PAX 135 mg/m2 plus CDDP,
- PAX 175 mg/m2 plus CDDP,
- PAX 250 mg/m2 plus CDDP,
- docetaxel (DOC) first line, and
- DOC second line.

The dosage was reported as mg per square metre (mg/m2) body surface area. The authors stated that common trial dosages were used in the economic model, but apart from PAX these were not explicitly reported.

Type of intervention
Treatment and palliative care.

Economic study type
Cost-effectiveness analysis.

Study population
The study population was patients with non small-cell lung cancer, with staging unspecified.

Setting
The setting was tertiary care (specialised centres and palliative care). The economic analysis was conducted in the UK.

Dates to which data relate
The price year was 1999 to 2000. The effectiveness evidence was published between 1993 and 2000. The resource use was published between 2000 and 2001.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies.

Outcomes assessed in the review
The systematic review assessed median survival, 1- and 2-year survival, quality of life parameters, and the incidence of adverse events. Only median survival was used as an input to the economic model.

Study designs and other criteria for inclusion in the review
The search strategy was reported elsewhere (see Other Publications of Related Interest no.1). Randomised controlled trials (RCT) of PAX, DOC, GEM and VIN, used separately or in combination in the treatment of patients with lung cancer, were included. The studies had to include either BSC, other new regimens, older regimens or platinum-based combination regimens. Only studies reported in the English language were included.

Sources searched to identify primary studies
Eleven databases including MEDLINE, the Cochrane Library, EMBASE and Cancer Trials were searched. Unpublished studies, identified from bibliographies of related publications or through contact with experts and industry, were also included. Abstracts or conference only publications were excluded.

Criteria used to ensure the validity of primary studies
Quality was assessed using the scale of Jadad et al. (see Other Publications of Related Interest no.2), which gives an integer score between 1 (lowest quality) and 5 (highest quality).

Methods used to judge relevance and validity, and for extracting data
Quality was assessed by one reviewer and checked by a second reviewer, with any differences being resolved by consensus.

Number of primary studies included
Thirty-three RCTs were used to assess clinical effectiveness.

Methods of combining primary studies
The authors stated that a meta analysis was not undertaken because of the diversity of the interventions and comparators. Also, because of differences in or insufficient detail on the outcomes used, patient characteristics, and drug dose and administration. A narrative method was used instead. In the economic model, median survival by regimen was aggregated using the number of patients as the weight.

Investigation of differences between primary studies
The differences among the RCTs were discussed in the narrative, although it was not suggested how these differences affected the estimate of the effectiveness of the technology.

Results of the review
The median survival in months for each regimen (aggregated data) was:
for BSC, 5.24;
for GEM, 6.90;
for GEM plus CDDP, 8.80;
for VNB, 7.06;
for VNB plus CDDP, 8.45;
for PAX, 6.51;
for PAX 135 mg/m2 plus CDDP, 9.40;
for PAX 175 mg/m2 plus CDDP, 8.81;
for PAX 250 mg/m2 plus CDDP, 10.00;
for DOC, 6.00; and
for DOC second line, 5.94.

The results for each RCT, along with 95% confidence intervals and p-values were tabulated in the original paper. The length of follow-up in the trials was not stated.

**Measure of benefits used in the economic analysis**
The outcome measure used was life-years saved.

**Direct costs**
The costs were those incurred by the hospital in order to provide the treatment. It was not stated how long the treatments lasted, only that each treatment required 3 or 4 cycles. Discounting was not applied to the costs. The resource use and the unit costs were not described in detail, and were not reported separately. The costs of the treatments were estimated from published and unpublished data. The costs of BSC were estimated by analysing the case notes from 36 patients with lung cancer. The authors stated that the costs of inpatient care, outpatient care, home visits and treatment costs were included, but provided no further details. The costs were reported as average and incremental (relative to BSC only).

**Statistical analysis of costs**
The costs were not treated stochastically.

**Indirect Costs**
The indirect costs were not included.

**Currency**
UK pounds sterling ().
a probability of 60% that a patient would not complete the full course;

a discount on the list price of the drugs;

an increase in the price of anti-emetics; and

the best and worst median survival time used in the trials

**Estimated benefits used in the economic analysis**
The incremental benefits, as median survival in months, were reported in the 'Results of the Review' section. The study converted these to the expected gain in life-years saved, by dividing these results by twelve. The side effects of treatment were not considered in the measurement of the economic benefit.

**Cost results**
The average cost per patients was reported as:

3,324 for BSC,

4,132 for GEM,

6,321 for GEM plus CDDP,

3,963 for VNB,

4,736 for VNB plus CDDP,

8,293 for PAX,

6,304 for PAX 135 mg/m2 plus CDDP,

7,550 for PAX 175 mg/m2 plus CDDP,

8,147 for PAX 250 mg/m2 plus CDDP,

5,040 for DOC, and

4,365 for DOC second line.

It was not stated how the costs of adverse events were treated in the costing.

**Synthesis of costs and benefits**
The incremental cost per life-year saved (compared with BSC in each case) was reported as:

5,690 for GEM,

10,041 for GEM plus CDDP,

4,091 for VNB,

5,206 for VNB plus CDDP,

46,610 for PAX,

8,537 for PAX 135 mg/m2 plus CDDP,
14,124 for PAX 175 mg/m² plus CDDP,
12,104 for PAX 250 mg/m² plus CDDP,
26,707 for DOC, and
17,546 for DOC second line.

A univariate sensitivity analysis showed that the cost-effectiveness was improved by reducing the number of cycles per
treatment, with 60% of patients completing only half a course, reducing the price of the drugs, and using the best
survival time for trial data.

**Authors’ conclusions**
Gemcitabine (GEM), paclitaxel (PAX) and vinorelbine (VIN) as first-line treatments, and docetaxel (DOC) as second
line, appeared to be beneficial to patient survival and quality of life, particularly when used as combination treatments.
Improvements in survival were from 2 to 4 months above survival for untreated patients of about 5 months. Gains in
survival were not at the expense of quality of life.

The regimens with the lowest incremental cost-effectiveness ratios relative to best supportive care (BSC) were VIN,
VIN plus cisplatin (CDDP), and GEM. The authors stated that the results were robust to a sensitivity analysis. The
authors stated that the cost-effectiveness of GEM plus CDDP and PAX plus CDDP were reasonable. PAX and DOC
were relatively expensive, while DOC as second line was expensive relative to BSC.

**CRD COMMENTARY - Selection of comparators**
The comparator was BSC. The choice excluded chemotherapy with older drugs, and the description of the care was
somewhat vague. The reader will need to decide whether this is appropriate for their circumstances.

**Validity of estimate of measure of effectiveness**
The authors undertook a systematic review of the literature. The review appears to have been reported in detail, and
another reference containing the search strategy was supplied. The authors stated that a meta-analysis could not be
conducted because the studies were too heterogeneous, but they then calculated a simple weighted mean of median
survival times as an input to the model. The authors did not discuss whether their method of aggregation was
appropriate. The authors recognised that the method of pooling the trial results consisted of indirect comparisons and
may have been open to confounding. For example, by different baseline characteristics of the trial populations. This
may lead to bias in the results.

The authors acknowledged that some studies did not report findings on an intention to treat basis, and that, given the
high rate of attrition from the trials, this may have led to bias. No attempt was made to compensate for this in the
analysis.

**Validity of estimate of measure of benefit**
The calculation of life expectancy requires the mean, not the median, of the survival time of patients using the
treatment. The effect of using the median instead of the mean was not discussed.

The authors acknowledged the limitations arising from not including quality of life in the model. They recognised that a
proportion of patients would choose to forego treatment in order to avoid side effects, but reported that there was also a
lack of understanding among patients about the side effects of chemotherapy.

**Validity of estimate of costs**
The cost boundary appears to have been limited to that of the tertiary provider. This is a narrow perspective, which does
not include a wide range of costs that potentially could be incurred by other elements of the health service.
The study did not provide sufficient detail for the reader to understand how the estimates of costs were calculated. Some one-way sensitivity analyses were conducted, by reducing the price of the drugs, increasing the price of anti-emetics, and changing the cost of BSC.

The authors considered that the costs of routine care would be much lower than those derived using data from trials. This is because in routine care, physicians would review continuation on a course by course basis and discontinue treatment for patients who were not responding. A major flaw was that the incremental analysis was incorrectly performed. BSC was used as the comparator for all other technologies. However, it is clear that several technologies would have been dominated (higher cost and lower effectiveness). These include those using GEM. In fact, the authors cite GEM as the most cost-effective. Once dominated technologies have been eliminated, the VIN technologies would have the lowest cost increase per gain in life-years. The PAX 135 and 250 mg/m2 technologies would be more effective, but at a higher increase in cost.

**Other issues**
The authors claimed that VIN and GEM as single and combination therapies, and PAX as combination therapy, are cost-effective. However, they did not make any explicit statement about the cost-effectiveness ceiling ratio that was applied in order to make these judgements, although it appears from the data to have been less than 30,000 per life-year saved.

The sensitivity analyses were limited to univariate analysis. The analyses based on reducing the number of cycles of treatment assumed that this did not affect the effectiveness in terms of survival.

The authors did not compare the results of the model with other studies. The authors did not believe the quality of some of the RCTs found to be high, with limited reporting of baseline characteristics. They advise that this may limit generalisability to other settings.

**Implications of the study**
The authors conclude that the clinical benefits from the new drugs are relatively small, but still worthwhile to patients, and cost-effective. They recommend more research of different combinations of treatments among sub-groups of patients, the use of treatments alongside radiotherapy, an assessment of quality of life, a comparison with non-drug treatments, and a prospective economic analysis. It must be noted that the authors' recommendations are not entirely supported in terms of whether the technologies are cost-effective, given the incorrect incremental analysis (see commentaries above for details).

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**Other publications of related interest**

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