Paclitaxel plus carboplatin versus gemcitabine plus paclitaxel in advanced non-small-cell lung cancer: a phase III randomized trial


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
Paclitaxel plus carboplatin (PC) and paclitaxel plus gemcitabine (PG) were compared for the treatment of patients with advanced non-small-cell lung cancer (NSCLC). The patients received paclitaxel (200 mg/m²) on day 1 plus either carboplatin at an area under the concentration-time curve of 6 on day 1 (group A) or gemcitabine (1,000 mg/m²) on days 1 and 8 (group B) every 3 weeks.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients (older than 18 years) with inoperable (historically documented, inoperable, recurrent, or metastatic) NSCLC. Patients with stable brain metastasis were eligible. In addition, the patients had to have adequate bone marrow reserve and normal kidney and liver functions. Patients with active infection and a history of other neoplasms, cardiac disease, or pre-existing motor or sensory neuropathy, were excluded from the study.

Setting
The setting was secondary care. The economic study was carried out in Athens, Greece.

Dates to which data relate
The effectiveness data were collected from patients enrolled from February 1998 to September 2000. The price year used for the cost calculations was not specified.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
A retrospective analysis of the costs attributed to each arm was undertaken, based on the same patient sample as that used in the effectiveness study.

Study sample
A total of 509 patients (252 in group A and 257 in group B) were enrolled. In terms of power calculations, using a
significance level of 0.05 and assuming a constant hazard ratio of 0.67, there was a 95% probability of detecting a significant difference between regimens when 404 deaths were observed. Taking into consideration a 10% withdrawal rate, 440 patients were therefore needed to detect a 50% increase in median survival, to a control median of 11 months. The number of patients who refused to participate was not reported.

**Study design**
The study was a randomised controlled trial (RCT) that was conducted in multiple centres (Hellenic Cooperative Oncology Group - 19 institutions). Randomisation was performed centrally. The patients were assigned to one of the two arms using the centre as a stratifying factor. The median time to follow-up for time to event measures was 20.7 months (range: 0.03 - 35.2+) for group A and 20.5 months (range: 0.07 - 30.4+) for group B. The median follow-up time for both groups combined was 20.7 months (95% confidence interval, CI: 18.0 - 21.5). Six patients (three from each group) were lost to follow-up.

**Analysis of effectiveness**
The authors did not state the criteria used to analyse the clinical data (intention to treat or treatment completers only). The primary outcomes were overall survival and 1-year survival times. The secondary assessment was to assess response, time to progression and toxicity profiles for both combinations in the treatment of patients with advanced inoperable NSCLC. All pre-treatment patient and disease characteristics were well balanced across the two groups of the study.

**Effectiveness results**
Median overall survival and time to progress (TTP) for groups A and B were not significantly different.

The overall median survival time was 10.4 months (95% CI: 8.8 - 12) for group A and 9.8 months (95% CI: 8.0 - 11.7) for group B, (p=0.36).

The median TTP was 6.3 months (95% CI: 5.6 - 7.1) for group A and 6.1 months (95% CI: 5.4 - 6.8) for group B, (p=0.36).

For groups A and B combined, median overall survival for those patients who had an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1 was significantly higher than for those with a PS of 2 (11.1 versus 5.9 months; p<0.0001), as was median TTP (6.6 versus 3.8 months; p<0.0001).

The median survival of patients with Stage III disease was significantly higher than that of patients with Stage IV disease (11.5 versus 8.9 months; p=0.002).

The respective 1- and 2-year survival rates were 41.7% and 17% for group A, and 41.4% and 15.2% for group B.

The multivariate analysis indicated that PS, (p=0.0001) and bone (p=0.002), supraclavicular lymph node, (p<0.0001), and liver involvement, (p<0.0001), were significant prognostic factors for 1-year survival.

Histology type or treatment did not affect survival.

The overall response rate was 35% with the PG regimen and 28% with the PC regimen.

The treatment was generally well tolerated in both groups, and no hospitalisations were required.

Overall, the haematologic toxicity profiles of groups A and B were similar.

There were no toxic deaths.

**Clinical conclusions**
The non-platinum PG combination demonstrated an activity and toxicity profile similar to the commonly used PC combination. The survival of patients with a PS of 2 was lower in both combinations.

**Measure of benefits used in the economic analysis**
No summary measure of benefits was reported. In effect, a cost-consequences analysis was performed.

**Direct costs**
Discounting of the costs was not carried out, which was appropriate as the median follow-up time was less than two years. The quantities and the costs were analysed separately. Outpatient clinic visits and drug costs were measured. The costs were estimated from actual data. The retrospective analysis of costs at the end of the study was based on 472 patients (232 in group A and 240 in group B). Dates for the quantities measured were the same as those for the effectiveness data. The price year was not stated.

**Statistical analysis of costs**
The costs were treated stochastically. Student's t-test was performed for group A versus group B.

**Indirect Costs**
No indirect costs were reported.

**Currency**
Euros (Euro).

**Sensitivity analysis**
No sensitivity analysis was carried out.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
Outpatient clinic expenses were significantly higher for group B (mean Euro 515) than for group A (mean Euro 289.7), (p<0.05).

The difference between the two groups in total chemotherapy drug cost was not significant, Euro 7,322.96 (standard deviation, SD=2,905.34) for group A versus Euro 6,969.73 (SD=3,378.88) for group B, (p=0.21).

When the total drug and outpatient clinic costs were combined, there was no significant difference between the groups, Euro 7,612 (SD=3,014.43) for group A versus Euro 7,484.77 (SD=3,378.88) for group B, (p=0.66).

No incremental costs were calculated. No adverse effects were included in the costing.

**Synthesis of costs and benefits**
Not applicable since a cost-consequences analysis was carried out.

**Authors' conclusions**
The non-platinum paclitaxel-gemcitabine (PG) combination demonstrated an activity and toxicity profile similar to the
commonly used paclitaxel-carboplatin (PC) combination. The survival of patients with a performance status (PS) of 2 was lower in both combinations. Although the PG combination required more outpatient clinic visits, its overall drug cost and, in particular, total expenses were similar to those of the PC combination.

CRD COMMENTARY - Selection of comparators
The comparator used was justified on the grounds that it was common practice in the authors' setting. You should decide if this represents a widely used technology in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on an RCT, which was appropriate given the study question. The study sample was representative of the study population. In addition, the patient groups were shown to be comparable at analysis. The method of randomisation, length of study and loss to follow-up were all reported, thus suggesting that the internal validity of the study is likely to be high. Appropriate statistical analyses were undertaken to account for potential biases and confounding factors. Power calculations were reported and an appropriate sample size was used.

Validity of estimate of measure of benefit
As the effectiveness analysis demonstrated that the two treatments were equally effective, only the costs were assessed further. Therefore, no summary measure of benefit was derived. The reader is thus referred to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
The authors did not state the perspective adopted for the analysis, but it seems to have been that of a single provider. As such, all the relevant costs appear to have been included in the analysis (drug costs and outpatient visit costs) as no hospitalisation or supportive measures were required. The costs and the quantities were reported separately, thus enhancing the reproducibility of the study in other settings. In addition, an appropriate statistical analysis of the quantities was performed. However, a mean cost value appears to have been used to calculate outpatient visit costs, but there were no details of what this mean value included. Therefore, it was unclear whether any relevant categories of costs were excluded and if any bias was introduced into the cost calculation. In this sense, differences in outpatient costs come only from differences in the number of visits. Moreover, the source and/or price year were stated for drug prices. No sensitivity analyses of the quantities or costs were conducted, which may limit the interpretation of the study findings.

Other issues
The authors compared their findings with those of other studies (see 'Other Publications of Related Interest' below for bibliographic details). They did not, however, directly address the issue of the generalisability of the results to other settings. The authors do not appear to have presented their results selectively and their conclusions seem to reflect the scope of the analysis. Finally, the authors recognised that the retrospective analysis of the costs "is not the most scientifically rigorous method for cost analysis", but this particular issue seems unlikely to have impacted on the results of this study.

Implications of the study
In terms of clinical practice, the results suggest that the PG combination is equally as active and well tolerated as the PC combination in patients with advanced NSCLC. Overall, no difference in economic benefit or cost was found between PC and PG.

Source of funding
None stated.
Bibliographic details

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Other publications of related interest


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Subject indexing assigned by NLM

MeSH
Adult; Aged; Aged, 80 and over; Antineoplastic Combined Chemotherapy Protocols /adverse effects /economics /therapeutic use; Carcinoma, Non-Small-Cell Lung /drug therapy /mortality; Cisplatin /administration & dosage; Deoxycytidine /administration & dosage /anals & derivatives; Disease-Free Survival; Female; Greece /epidemiology; Health Care Costs; Humans; Logistic Models; Lung Neoplasms; Male; Middle Aged; Multivariate Analysis; Paclitaxel /administration & dosage; Retrospective Studies; Survival Rate

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