The cost-effectiveness of four cisplatin-containing chemotherapy regimens in the treatment of stages III B and IV non-small cell lung cancer: an Italian perspective

Palmer A J, Brandt A

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
Cisplatin-containing chemotherapy regimens in the treatment of stages III B and IV non-small cell lung cancer (NSCLC): gemcitabine+cisplatin (G+C), mitomycin+ifosfamide+cisplatin (MIP), etoposide+cisplatin (E+C) and vinorelbine+cisplatin (V+C).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
An hypothetical cohort of patients treated with cisplatin-containing chemotherapy regimens (G+C, MIP, E+C and V+C) in the treatment of stages III B and IV non-small cell lung cancer (NSCLC).

Setting
Hospital. The economic study was carried out in Switzerland. The cost-effectiveness was assessed with respect to the situation in Italy.

Dates to which data relate
The main effectiveness data were obtained from previously completed studies conducted between 1989 and 1995 and from a survey of two experts in the field of NSCLC chemotherapy. Resource and cost data were taken from 1994-95 sources. The price year was not stated.

Source of effectiveness data
The estimates of efficacy and safety data for the regimens were obtained from previously completed studies and from a survey of experts’ opinions.

Modelling
A disease model was used in the form of an influence diagram and a decision tree (DPL software).

Outcomes assessed in the review
Efficacy and safety data for each regimen were assessed.
Study designs and other criteria for inclusion in the review
A search was made for trials with patient populations in terms of disease staging, previous curative radiotherapy, previous chemotherapy and performance status which may affect the tumour response rate, the incidence of chemotherapy side-effects and patient survival. The main inclusion criteria were that studies should have the following combination chemotherapies in at least one treatment arm: G+C, MIP, E+C, V+C, and with doses comparable to the current Italian regimen.

Sources searched to identify primary studies
A MEDLINE search was performed using the search terms: gemcitabine, etoposide, MIP, vinorelbine, each in combination with non-small cell lung cancer and each in combination with clinical trial and review for the period between 1966 and 1995. Articles with a high probability of relevance were retrieved. An extensive manual search was performed of the references in the articles retrieved and articles with a high probability of relevance identified in this way were also retrieved.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
The authors reviewed 22 studies in total. Seven studies were included. One study with one G+C treatment arm, one study with one MIP treatment arm, three studies with one E+C treatment arm and two studies with one V+C treatment arm were included.

Methods of combining primary studies
Narrative method. When efficacy and safety results for the same regimen were reported in more than one study, the values were combined using a random effects meta-analysis method (the Der Simonian and Laird random effects meta-analysis model using Fast*Pro software). In cases where a particular outcome parameter was reported in only one study for a particular treatment and for which no 95% confidence intervals (CI) were reported, 95% CI were calculated (Fast*Pro software). Two of the studies reported different subsets of information about the same patient group and the results for these two reports were therefore combined.

Investigation of differences between primary studies
Only one G+C and only one MIP study were included in the analysis. The MIP study and the three E+C studies did not state any values for the percentage of patients with WHO grade 3 and 4 neutropenia. As an estimate, the value stated for leukopenia was used for neutropenia for these two treatments. One of the two studies on V+C reported only a combination of grade 2-4 WHO toxicities for renal toxicity, diarrhoea and local injection site reactions.

Results of the review
Overall tumour response rate was 54%, 40%, 23%, 26%, 27%, 30% and 43% for the single G+C and MIP study, the three studies on E+C and the 2 studies on V+C, respectively. The percentage of patient suffering WHO grade 3 and 4 toxicity were reported in details in a table.

Methods used to derive estimates of effectiveness
Authors’ assumptions and a survey of two experts in the field of NSCLC chemotherapy were also used to derive estimates of effectiveness.
Estimates of effectiveness and key assumptions
It was assumed that one third of the patients suffering from WHO grades 3 and 4 nausea and vomiting would be admitted to hospital. Regimens for the administration of G+C, MIP, E+C and V+C used in Italy and standard concomitant medications administered with each type of chemotherapy, including prophylactic antiemetics, bladder protectants and prehydration, were assumed. The estimates for the doses of cisplatin and other chemotherapy and the cycle length were:

- G+C, gemcitabine 1,000 mg/m² days 1-8-15 + cisplatin 100 mg/m² day 2 in 4 week cycles;
- MIP, mitomycin C 6 mg/m² day 1 + ifosfamide 3 g/m² day 1 + cisplatin 120 mg/m² day 2 in 3 week cycles;
- E+C, etoposide 100 mg/m² days 1-2-3 + cisplatin 120 mg/m² day 1 in 3 week cycles;
- V+C, vinorelbine 30 mg/m² days 1-8-15 + cisplatin 80-100 mg/m² day 1 in 3-6 week cycles.

Measure of benefits used in the economic analysis
The measure of benefits was tumour response rate.

Direct costs
Medical costs of four cycles of chemotherapy and the costs of management of the WHO grades 3 and 4 toxicities for each chemotherapy regimen were included in the analysis. The quantities were reported separately from the prices. The quantity/cost boundary adopted was the third party payer (government reimbursement) based on the disease-related groups (DRG) values for hospital admission for the administration of chemotherapy, the management of chemotherapy-associated WHO grades 3 and 4 toxicities and the reimbursement values of the chemotherapy and concomitant medications specific to each chemotherapy regimen, as stated in the official reimbursement publication. Discounting was not undertaken as the majority of stages IIIB and IV NSCLC patients do not survive beyond one year. The minimum, mean and maximum expected direct costs were calculated for each treatment.

Statistical analysis of costs
P values and 95% CI.

Indirect Costs
Not considered.

Currency
Italian Lira (L).

Sensitivity analysis
A one-way sensitivity analysis of the average cost-effectiveness was performed on each parameter in the model (cost values, efficacy and toxicity). Additionally, an "analysis of the extremes" was performed: the lowest and the highest average cost-effectiveness ratios were calculated.

Estimated benefits used in the economic analysis
The mean tumour response rates were: 54% (95% CI: 40-69%) for G+C, 40% (95% CI: 32-49%) for MIP, 26% (95% CI: 20-30%) for E+C and 35% (95% CI: 24-48) for V+C.
Synthesis of costs and benefits
Average and incremental (marginal) cost per tumour response showed that the use of MIP, E+C or V+C instead of G+C would result in additional costs of 7.7, 55.2 (p<0.05) and 46.2 million lira, respectively, for every patient with a tumour response. The minimum and maximum expected average cost-effectiveness ratios for each treatment were (Italian lira): 48.5 and 147.1, 59.2 and 143.4, 65.6 and 253.9, 81.4 and 225.4, for G+C, MIP, E+C and V+C, respectively. When the G+C tumour response rate was varied between the upper and lower limits of the 95% CI confidence intervals, the average cost-effectiveness ratio varied from 65.3 million to 91.0 million Italian lira, respectively. When the probability of neutropenia using G+C was varied between 0.245 and 0.514, the average cost-effectiveness ratio varied from 78.2 to 89.6 million Italian lira per tumour response, respectively. When the probability of anaemia using G+C was varied between 0.15 and 0.40, the average cost-effectiveness ratio varied from 79.2 to 89.8 million Italian lira, respectively.

Authors’ conclusions
G+C is significantly more effective than E+C in terms of tumour response and tends to be more effective than MIP and V+C. G+C chemotherapy tended to incur higher direct medical costs when used in chemotherapy stage III B and IV NSCLC in comparison with MIP and E+C but lower than V+C, although the differences were not significant. Average cost-effectiveness analysis showed a trend towards greater cost-effectiveness of G+C in comparison to MIP, E+C and V+C. Marginal cost-effectiveness analysis demonstrated a significant advantage for G+C in comparison to V+C, a trend towards greater cost-effectiveness of G+C in comparison to E+C and a non-significant trend towards greater cost-effectiveness of G+C in comparison to MIP. Tumour response rate was identified as the parameter with the greatest single influence on the average cost-effectiveness ratio. The probability of neutropenia and the probability of anaemia were the factors with the second and third most influence on the cost-effectiveness ration.

CRD COMMENTARY - Selection of comparators
The reason for the choice of comparators is clear. Chemotherapy for stages III B and IV NSCLC is associated with potentially severe toxic side-effects, which result in the consumption of significant health care resources. G+C has been shown to have at least equal efficacy and possible advantages in terms of less severe toxicities in comparison with alternative chemotherapy regimes which in turn might result in a decreased consumption of health resources. Therefore, G+C chemotherapy was compared to the most common regimes for NSCLC in Italy: MIP, E+C and V+C. You, as user of this database, should consider whether these are widely used health technologies in your own setting.

Validity of estimate of measure of benefit
The estimates of benefit are likely to be internally valid as the authors conducted a systematic review in deriving effectiveness data for the model. The data do not appear to have been used selectively. However, in employing a model the study suffers from the well-accepted limitations of using hypothetical patients.

Validity of estimate of costs
Resource quantities were reported separately from the prices. Adequate details of methods of quantity/cost estimation were given and important cost items do not appear to have been omitted. However, the costing methodology lacked some details and the price data was not stated.

Other issues
The validity of the study results may have some limitations given that, as the authors stated, the retrospective nature of the study required a number of assumptions to be made concerning the antiemetic prophylaxis regimen used, the number of cycles of chemotherapy administered, the admission of patients for administration of chemotherapy and the use of DRG values for hospitalisation costs. The issue of generalisability to other countries was not addressed. The inclusion criteria were designed to capture studies with comparable patient populations and which reflect current Italian NSCLC chemotherapy regimes. The modelled solutions were tested using one-way sensitive analysis in order to validate the robustness of the findings. Appropriate comparisons were made with other studies as a systematic review of relevant literature was conducted, particularly in relation to efficacy and safety data for the regimes. However, as noted by the authors, these results should be interpreted with some caution given the limited number of trials in each
Implications of the study
Further research is required within the context of a prospective clinical trial to provide more concrete evidence for a clinico-economic comparison of these treatment regimens and a more accurate analysis of costs and cost-effectiveness of these treatments. Moreover, further studies are required in assessing consumption of health resources for WHO grades 1 and 2 toxicities.

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Bibliographic details

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Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
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