Economic evaluation in a randomized phase III clinical trial comparing gemcitabine/cisplatin and etoposide/cisplatin in non-small cell lung cancer

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
Gemcitabine/Cisplatin (GC) and Cisplatin/etoposide (EC) as chemotherapeutic agents in the treatment of non-small cell lung cancer. The GC treatment involved gemcitabine 1250 mg/m^2 intravenously once a week for two weeks (days 1 and 8) plus cisplatin 100mg/m^2 intravenously on day 1 of each 21-day cycle, administered before the gemcitabine infusion. The EC treatment involved etoposide 100mg/m^2 intravenously on days 1, 2 and 3 plus cisplatin 100mg/m^2 on day 1 of each 21-day cycle, administered before the etoposide infusion.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Patients with a histologic or cytologic diagnosis of NSCLC, stages III or IV (according to the American Joint Committee on Cancer, 1992), at least 18 years of age, with a Karnofsky performance status greater than 60, a life expectancy greater than 12 weeks, and adequate bone marrow, renal and hepatic function.

Setting
Secondary care (hospital). The economic study was conducted in Spain.

Dates to which data relate
Efficacy data were derived from an RCT, the results of which were published in 1999. Dates for resource use data and the price year were not given.

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

Link between effectiveness and cost data
Care resource utilisation data were collected prospectively on the same patient sample as that used in the effectiveness study.

Study sample
Of the 135 patients enrolled into the study, 69 were randomised to the GC group and 66 to the CE group. Randomisation was stratified on four factors: gender, performance status, disease stage and investigation centre.
patients in the GC arm were qualified for efficacy analysis, 2 patients dropped out of the EC arm. Thirty patients in the GC arm (43%) and 17 in the EC arm (26%) received up to six cycles of treatment. The median duration of the treatment was 4.1 months in the GC group and 3.1 in the EC group. The median number of cycles administered was 5 for the GC group and 4 for the EC group.

**Study design**
This was an open-label, multicentre, randomised, comparative, phase III trial that compared gemcitabine/cisplatin and cisplatin/etoposide in chemonaive patients with stage IIIB or IV NSCLC.

**Analysis of effectiveness**
Objective tumour response was the primary criterion in both arms. The standard World Health Organisation (WHO) criteria were included in the evaluations: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). All tumour responses were confirmed through a peer review process by two independent radiologists. Time to disease progression and survival were secondary end points. Time to disease progression was measured as the time from randomisation to the date the patient was assessed as having progressive disease. Survival was defined as the interval from the date of randomisation to the date of death or date of last contact if lost to follow-up. Both treatment arms were shown to be well balanced with respect to baseline demographic and disease characteristics.

**Effectiveness results**
The effectiveness results were as follows:

Patients in the gemcitabine arm had an estimated median survival time of 8.7 months, (95% CI: 7.7 - 10.2 months) compared with an estimated median survival of 7.2 months, (95% CI: 6.1 - 9.8 months) for patients in the etoposide arm. The difference between the two arms was not statistically significant.

There were 28 responders in the gemcitabine arm for a response rate of 40.6%, (95% CI: 29% - 53%) and 14 responders in the etoposide arm for a response rate of 21.9%, (95% CI: 13% - 34%), (p=0.02; two sided, Fisher’s Exact Test).

The median time to progression for patients in the gemcitabine arm was 6.9 months, (95% CI: 5 - 8.1 months) compared to 4.3 months, (95% CI: 3.5 - 4.7 months) for patients in the etoposide arm. The log-rank test showed a statistically significant difference between the two curves, (p=0.01).

**Clinical conclusions**
Patients treated with gemcitabine had a longer estimated survival, a better response rate and a longer time for progression than those in the etoposide arm had.

**Measure of benefits used in the economic analysis**
There were no differences between both regimes when survival was the main end point; therefore the authors undertook a cost-minimisation analysis to compare the costs of both treatments. Additional measures of health benefit, namely the endpoints additional response and progression free month (which had statistically significant differences) were used in a cost-effectiveness analysis.

**Direct costs**
The perspective of the analysis was that of the Spanish health care payer. Direct costs considered in the analysis included: hospitalisations (number of days due to drug administration, adverse events, diagnostic procedures, febrile neutropenia, and other reasons), transfusions, health care professional visits, (oncologist, general physician, emergency room, other visits), chemotherapy administration, concomitant medications, and radiotherapy. Since treatment did not
extend beyond one year, discounting was not necessary. The unitary costs were estimated based on governmental and hospital data. Quantities and costs were reported separately. The price year was not stated.

**Statistical analysis of costs**

None of the direct medical costs were distributed normally, (p<0.05 when using the Kolmogorov-Smirnov test), therefore analysis of differences between the costs of the groups was carried out using the non-parametric Mann-Whitney U test.

**Indirect Costs**

No indirect costs were considered.

**Currency**

Spanish pesetas (ptas) at 1997 prices (US$1 = ptas145).

**Sensitivity analysis**

Sensitivity analyses were performed with cost of hospitalisation being selected as the most relevant cost that could change in Spanish settings. Hospitalisation costs were varied from B25 to + 50% with respect to baseline costs. As resource use and cost data are often skewed because of relatively small number of patients with additional resources and costs, a bootstrapping method, which does not require parametric distributional assumptions, was used.

**Estimated benefits used in the economic analysis**

See effectiveness results above.

**Cost results**

The direct medical costs reported for both treatments (mean +/- SD) were:

- **Gemcitabine/cisplatin group:** chemotherapy (ptas229,144 +/- 79,329), antiemetics (ptas26,528 +/- 24,299), hospitalisation (ptas187,252 +/- 240,560), medical visits (ptas133,600 +/- 51,309) and transfusions (ptas7,999 +/- 14,028);

- **Cisplatin/etoposide group:** chemotherapy (ptas44,047 +/- 19,361), antiemetics (ptas31,618 +/- 35,662), hospitalisation (ptas351,663 +/- 549,770), medical visits (ptas151,941 +/- 72,171) and transfusions (ptas10,810 +/- 28,654).

**Synthesis of costs and benefits**

Cost minimisation was used to compare the cost of both treatments when survival was used as the main end-point. Total medical costs were similar for both treatments so they could be considered equivalent regimens from a health economic perspective. When efficacy was measured as a percentage of responses, average cost effectiveness was ptas1,439,712 for gemcitabine and ptas2,692,374 for etoposide. A negative incremental cost-effectiveness ratio (ICER) (-27,310) resulted per additional tumour response with gemcitabine versus etoposide. Gemcitabine/cisplatin was also the dominant option when time to progression was used as the final end-point (-3,405ptas/progression free month). Cost per progression free month was ptas84,713 for gemcitabine and ptas137,123 for cisplatin.

**Authors' conclusions**

The authors suggest that the higher chemotherapy cost of gemcitabine/cisplatin when compared to cisplatin/etoposide does not imply an increased direct cost, as potential savings associated with a decrease in hospitalisation costs arise from the use of gemcitabine. Differences exist in favour of GC when response rate and time to disease progression are used as clinical end-points, but this was not extended to survival.
CRD COMMENTARY - Selection of comparators
The author's choice of etoposide/cisplatin as a comparator was justified. Data suggest that gemcitabine/cisplatin seemed to be more effective than gemcitabine alone and additionally, available data suggest that gemcitabine alone is better tolerated than cisplatin/etoposide and that gemcitabine/cisplatin has an acceptable tolerability profile.

Validity of estimate of measure of benefit
The analysis was based on a prospective randomised trial, which was appropriate for the study question. The study sample was representative of the study population. Patient groups were shown to be comparable at analysis. The analysis of benefits was based on the therapeutic equivalence of treatment alternatives, therefore a cost minimisation analysis was carried out. A cost-effectiveness analysis was undertaken and the estimation of benefits was obtained directly from the effectiveness analysis. This choice of estimate was justified.

Validity of estimate of costs
Although the authors reported that costs were estimated from the Spanish health care payer perspective, no indirect costs were included, which may limit the generalisability of the results to other settings and health systems. Costs related to research (protocol driven costs) were excluded. In order to correct for the experimental trial environment those visits required by the protocol were excluded as they could not be considered standard care. Costs and quantities were reported separately. A sensitivity analysis was conducted. The ranges used appear to have been appropriate.

Other issues
The authors did make appropriate comparisons of their findings with those from retrospective pharmaco economic studies conducted with gemcitabine. The authors do not appear to have presented their results selectively. The authors reported a number of limitations to their study, in particular that tumour response rate may not be the optimum efficacy measure in oncology, and, ideally, that comparisons should be based on robust long-term efficacy measures such as survival. The authors also acknowledged that the sample size was not chosen to demonstrate a survival difference, as there was insufficient power to do so.

Implications of the study
The authors call for their results to be validated in larger clinical trials focussed on survival and naturalistic economic studies conducted in real clinical settings (to determine effectiveness as opposed to efficacy).

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