Chemotherapy versus supportive care in advanced non-small cell lung cancer: improved survival without detriment to quality of life


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
Two strategies for supporting patients with advanced non small-cell lung cancer (NSCLC) were examined. The strategies were supportive care alone (SC) and SC plus chemotherapy (CHEM). SC included palliative radiotherapy. CHEM consisted of palliative radiotherapy plus three cycles of 3 weekly cisplatin-based chemotherapy. Four cisplatin regimens were considered

MIC: day 1: cisplatin 50 mg/m2, mitomycin 6 mg/m2, ifosfamide 3 g/m2.

MVP: day 1: cisplatin 50 mg/m2, mitomycin 6 mg/m2, vinblastine 6 mg/m2.

CV: day 1: cisplatin 80 mg/m2, vindesine 3 mg/m2; day 8: vindesine 3 mg/m2.

NP: day 1: cisplatin 80 mg/m2, vinorelbine 30 mg/m^2; day 8: vinorelbine 30 mg/m2.

Type of intervention
Other: Supportive care.

Economic study type
Cost-effectiveness analysis.

Study population
The study population included patients fulfilling criteria for histological or cytological diagnosis of NSCLC. Further inclusion criteria were patients being considered unsuitable for, or refusing, radical radiotherapy or surgery, and patients considered fit to receive chemotherapy. Another criterion was no concurrent malignancy or history of malignancy, other than non-melanomatous skin cancer within the last 3 years.

Setting
The setting was a hospital. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness and resource use data were gathered from November 1995 to November 2001. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study.
Link between effectiveness and cost data
The costing was carried out retrospectively on a sub-group of patients who were involved in the clinical study.

Study sample
Power calculations were carried out in the preliminary phase of the study. These suggested that a total sample of 800 patients was required to reliably detect an improvement in median survival from 4 months with SC alone to 5 months with CHEM (80% power, 5% significance). Power calculations were carried out also for the secondary outcome, that is, quality of life. It was noted that approximately 300 patients were required to detect a large difference in quality of life (which physicians regarded as clinically meaningful) with 80% power and 5% significance. A study sample of 725 patients was enrolled into the trial. There were 364 patients in the CHEM arm and 361 patients in the SC arm. The CHEM arm comprised 76% men, 38% in clinical Stage IIIb and 38% in clinical Stage IV. The SC arm comprised 72% men, 31% in clinical Stage IIIb and 39% in clinical Stage IV. The median ages of the patients were 65.2 years (CHEM arm) and 65.8 years (SC arm). The quality of life sub-study involved 273 patients, 135 in the CHEM group and 138 in the SC group.

Study design
This was a prospective, multi-centre, randomised clinical trial. The patients were identified at 57 UK and 5 non-UK centres. The authors stated that the choice of chemotherapy regimen (from one of four cisplatin-based regimens) could be made on a patient-by-patient basis, but the choice had to be stated before randomisation. The patients were stratified by centre, choice of chemotherapy regimen, gender, histology, performance status, and whether the patient was taking part in the quality of life sub-study. The follow-up assessment was carried out at baseline, 3 months, 6 months, one year, and then annually. The average follow-up time for survivors was 23 months. No patient appears to have been lost to follow-up. The outcome assessment was not reported to have been blind.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The main outcome measure was survival, which was estimated using the Kaplan-Meier method. Sub-groups of patients were compared in terms of their hazard ratios and confidence intervals (CIs). A secondary outcome measure was global quality of life, which was assessed at 12 weeks post-randomisation using the EORRC QLQ-C30 and LC17 questionnaires. Characteristics of the CHEM and radiotherapy regimens were accurately described. The study groups were comparable at baseline in terms of their clinical and demographic characteristics.

Effectiveness results
The most commonly used CHEM regimens were MIC and MVP. Of the 364 patients allocated to receive CHEM, 238 (65%) received their prescribed three cycles of the regimen chosen before randomisation. A further 42 patients (12%) received two cycles, 54 (15%) received one cycle, 24 (7%) received no chemotherapy, and 6 (2%) received a regimen different from that chosen. Significantly more SC patients received radiotherapy (74%) than CHEM patients (47%). The doses of radiotherapy received were similar in the two groups. Toxicity was much as expected for cisplatin-based regimens. Thirty-one per cent of patients were reported to have as experienced Grade 3/4 toxicity, mainly haematological (14%), nausea or vomiting (4%), neurological (2%) and renal (1%) toxicity. Patients receiving two-drug regimens experienced more Grade 3/4 toxicity than those on three-drug regimens (44% versus 28%). Reasons for stopping or not receiving CHEM were reported.

At the time of analysis 697 (96%) patients had died. The overall hazard ratio was 0.77 (95% CI: 0.66 - 0.89; p=0.0006). The median survival was 8.0 months for CHEM patients and 5.7 months for SC patients. One- and 2-year survival figures were 29% and 10%, respectively, with CHEM and 20% and 5% with SC.

A multivariate analysis showed that survival was related to stage and World Health Organization performance status. Patients with squamous histology survived longer than patients with adenocarcinoma. There was no evidence that survival was related to age, gender, or chosen CHEM regimen.
In the CHEM group, 298 (86%) of the patients who died were reported as dying of lung cancer, but there were 14 (4%) treatment-related deaths and 33 (10%) patients were reported as dying of other causes. In the SC group, 338 (96%) were reported as dying of lung cancer, in addition to one (0.3%) of a treatment-related cause and 13 (4%) of other causes. A detailed analysis of deaths from other causes was undertaken.

No statistically significant differences were observed between the groups in terms of quality of life. This meant that large positive or negative effects of CHEM were ruled out, especially for some dimensions of health such as fatigue and dyspnoea.

Clinical conclusions
The effectiveness analysis showed that CHEM improved survival in comparison with SC in patients with advanced NSCLC. Quality of life aspects were comparable between groups.

Measure of benefits used in the economic analysis
The summary benefit measure was the survival advantage observed in the clinical trial.

Direct costs
Discounting does not appear to have been relevant since costs incurred during a 2-year period were considered. The unit costs were not presented separately from the quantities of resources used. The health services included in the economic evaluation were number and duration of inpatient admissions, use of CHEM, radiotherapy details, investigations, outpatient visits, day cases, surgical procedures and hospice inpatient care. The cost/resource boundary adopted in the study was not stated. Resource used was estimated from a retrospective analysis of a sub-group of patients included in the clinical trial (99 patients in the CHEM group and 95 patients in the SC group). The resource use data were gathered from randomisation until death (or to 2 years if the patient was still alive at this time point). The source of the cost data was not reported. The price year was not reported.

Statistical analysis of costs
Statistical analyses were carried out to test the statistical significance of differences in the estimated costs. Power calculations were also carried out. These showed that 200 patients were required to detect an economically meaningful difference in the mean costs between the two groups with 80% power and a 5% level of significance.

Indirect Costs
The indirect costs were not included in the economic evaluation.

Currency
UK pounds sterling (€).

Sensitivity analysis
Sensitivity analyses were not carried out.

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

Cost results
The authors stated that the net difference between the groups was approximately equal to the cost of the chemotherapy drugs themselves (including drug administration), which was 1,268. There was no statistically significant difference
between the groups in all of the other costs combined (4,238 for CHEM and 3,718 for SC; p=0.3).

**Synthesis of costs and benefits**

An average cost-effectiveness ratio was calculated to combine the costs and benefits of the alternative strategies. The cost per week of life was 157 with CHEM and 149 with SC.

**Authors' conclusions**

The authors concluded that their findings confirmed the reported survival advantage associated with chemotherapy (CHEM) over supportive care (SC) alone in patients with non small-cell lung cancer (NSCLC). The analysis showed that CHEM did not have a negative impact on quality of life and, in general, CHEM was cost-effective.

**CRD COMMENTARY - Selection of comparators**

The selection of the comparators (SC and CHEM) reflected available treatment patterns. It was stressed that the analysis did not compare the four different CHEM regimens. The authors stated that the definition of SC was not defined in the protocol, but was left to the discretion of local clinicians. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness evidence came from a well-conducted clinical trial, which was appropriate for the study question. The internal validity of the study was high, owing to the characteristics of the study. First, power calculations were carried out for the two main outcome measures. Second, the study groups were comparable at baseline. Third, randomisation was stratified by key factors. Fourth, the analysis of the clinical study was conducted on an intention to treat basis. Fifth, a multivariate analysis was carried out to assess the impact of baseline factors. Finally, the evidence came from multiple centres and a sub-group analysis was undertaken. Such characteristics should reduce the impact of confounding factors and selection bias.

**Validity of estimate of measure of benefit**

The summary benefit measure was survival, which was appropriate and comparable with the benefits of other health care interventions. Discounting was not performed because of the poor life expectancy of the patients considered in the study.

**Validity of estimate of costs**

The analysis of costs represented a secondary aim of the study. Limited information on the economic data was provided in this paper (but note that more detail on this aspect can be found in Maslove et al 2005, see “Other Publications of Related Interest” below for bibliographic details). The unit costs, quantities of resources used, price year and source of data were not reported clearly. Power calculations were carried out and a sub-group of patients included in the clinical trial was considered in the cost analysis. The authors stated that the main characteristics of the cost analysis would shortly be published separately, while the preliminary results had already been published. Only the main economic results were presented.

**Other issues**

The authors compared their findings with those from other published studies in a narrative, and consistent results were observed. Explanations for differences between their study and other studies were provided. However, the issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were not carried out. This reduces the external validity of the analysis. The study referred to patients with advanced NSCLC and this was reflected in the authors' conclusions.
Implications of the study
The study results supported the use of CHEM for the treatment of patients with advanced NSCLC. The authors stressed that the additional information provided by their study should enable future patients and their clinicians to make more informed decisions about the treatment of NSCLC.

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Other publications of related interest


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