From randomised clinical trials to clinical practice: a pragmatic cost-effectiveness analysis of paclitaxel in first-line therapy for advanced ovarian cancer

Limat S, Woronoff-Lens M C, Menat C, Madroszyk-Flandin A, Merrouche Y

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 health intervention examined in the study was intravenous paclitaxel plus cisplatin (PC) for the treatment of women with advanced ovarian cancer (OC). The following doses were considered: intravenous paclitaxel (day 1, 135mg per m^2 as a 24-hour infusion) and cisplatin (day 2, 75mg per m^2 as a 3-hour infusion) once every 3 weeks.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised women with verified International Federation of Gynaecology and Obstetrics (FIGO) stage IIc, III or IV OC. Exclusion criteria included patients with localised disease, those aged over 80 years, and women who had received only one cycle of initial chemotherapy.

Setting
The setting was a university hospital. The economic study was carried out in France.

Dates to which data relate
Effectiveness and resource use data were gathered from 1995 to 2000. The price year was 2000, with the exception of hospitalisation costs that were estimated using 1999 values.

Source of effectiveness data
The effectiveness evidence came from a single study.

Link between effectiveness and cost data
The costing was carried out retrospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations were not performed. Initially a sample of 69 consecutive patients treated for OC were enrolled. Ten patients were excluded from the current analysis for different reasons (non-advanced stage in 5 women; doubt about the initial diagnosis in 2 patients; unevaluated disease for one woman, first-line chemotherapy partially administered in another centre for another woman, and only one cycle of chemotherapy received for a patient). From 1995 to 1997, 29 women received CC, while a sample of 30 women received PC from 1998 to 2000. The median age at diagnosis was
65.1 (range: 29 - 80) years in the CC group and 61.3 (range: 39 - 77) years in the PC group.

Study design
This was a retrospective comparative study with historical control, which was carried out at a single institution, namely the Besancon University Hospital in Besancon, France. The length of follow-up was not clearly reported. Some patients were followed up until death. No woman appears to have been lost to follow-up. Blinding was not performed.

Analysis of effectiveness
All patients included in the initial study sample were taken into account in the analysis of effectiveness. The primary outcome measures were OS, PFS, and quality of life, which was assessed using the quality-adjusted time without symptoms or toxicity (Q-TwiST) method, which was accurately described and was used to determine quality-adjusted life-years (QALYs). These measures were all estimated using the Kaplan-Meier approach. Other clinical outcomes were hospital stay (both continuous hospitalisations and day hospitalisations), cycles of chemotherapy, frequency of febrile neutropenia requiring hospitalisation, and blood product requirements. Study groups were comparable at baseline but age was significantly higher in the CC group.

Effectiveness results
The median PFS was 11.2 months in the CC group and 14.2 months in the PC group.

The median OS was 21.2 months in the CC group and 32 months in the PC group.

Using the Q-TwiST method, the median benefit was 11.3 months in the CC group and 21.6 months in the PC group, resulting in an estimated QALY gain with PC over CC of 0.775.

Mean continuous hospitalisation days were 14.3 with CC and 22.1 with PC, (p<0.001).

The length of day hospitalisation was 0.6 days with both treatments, (p=0.7).

No statistically significant differences in the mean number of chemotherapy doses, frequency of febrile neutropenia requiring hospitalisation, or blood product requirements were observed between groups.

Clinical conclusions
The effectiveness analysis showed that PC led to a greater (quality-adjusted) survival in comparison with CC among patients with advanced OC.

Measure of benefits used in the economic analysis
The summary benefit measures used in the economic analysis were QALYs and OS, which were estimated directly from the effectiveness analysis. The approach used to derive utility values (Q-TwiST method) was extensively described.

Direct costs
The analysis of costs was carried out from the perspective of the hospital payer and included the following categories of costs: hospitalisation for chemotherapy administration or management of febrile neutropenia; chemotherapy; supportive drugs (anti-infectious agents and haematopoietic growth factors; and blood products. Unit costs were presented separately from quantities of resources used. Quantities of resources used were estimated from the effectiveness study using patient medical records and validated by computerised data, whenever available. Unit costs were estimated from several sources, including official tariffs, the analytic accounting system at the University hospital, and wholesale prices from national price lists for drugs. Discounting was not relevant as costs were incurred over a short time frame. The price year was 2000, with the exception of hospitalisation costs that were estimated using 1999 values.
Statistical analysis of costs
Standard analyses of costs were carried out to test the statistical significance of cost differences between groups.

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

Currency
US dollars ($). Costs were estimated in French francs (FRF) and then converted into Euros (EUR) and US dollars at the following rate: $1 = FRF7 = EUR 1.067.

Sensitivity analysis
Extensive sensitivity analyses were carried out to assess the robustness of cost-effectiveness results to variations in clinical and economic data. The following analyses were performed:

incremental analyses were performed using trimmed mean and median costs;

costs of hospitalisation, drugs and blood products were varied by +/- 30%;

costs in the PC group were modelled assuming a shorter infusion of paclitaxel (paclitaxel at a dose of 175 mg/m^2 as a 3-hour infusion, requiring only 1 day of hospitalisation for each cycle);

the two regimens were considered to be administered in day hospitalisation, instead of continuous hospitalisation;

overall benefits were varied by +/- 30%.

Estimated benefits used in the economic analysis
Please refer to the effectiveness results reported above.

Cost results
Overall costs per patient were $6,798 (95% confidence interval (CI): $4,604 - $8,991; range: $2,336 - $34,172) in the CC group and $17,514 (95% CI: $15,317 - $19,769; range: $7,279 - $37,041) in the PC group, (p<0.0001). CC was characterised by significantly higher costs associated with hospitalisations, but PC patients incurred significantly higher costs for chemotherapy and associated with haematopoietic growth factors.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios and cost-utility ratios were calculated to combine costs and benefits of PC over CC.

The incremental cost per life-year gained with PC over CC was $11,907, while the incremental cost per QALY gained was $13,827.

The sensitivity analysis showed that the range of cost-effectiveness ratios was $8,358 to $17,010, while the range for cost-utility ratios was $9,706 to $19,753. The highest cost-effectiveness and cost-utility ratios were associated with the assumption of lower benefits with PC while the lowest cost-effectiveness and cost-utility ratios were obtained with the assumptions of higher unit costs of hospitalisation, drugs and blood products.

Authors' conclusions
The authors concluded that a PC regimen as first-line treatment for advanced OC is a cost-effective strategy in
comparison with CC from the perspective of a French university hospital.

CRD COMMENTARY - Selection of comparators
The authors justified the choice of the interventions examined in the study. The CC regimen represented the standard care before the introduction of PC, which was first administered at the authors' institution in 1998. Dosages were clearly reported and the impact of using alternative administration modalities was investigated in the sensitivity analysis.

Validity of estimate of measure of effectiveness
The effectiveness evidence was obtained using a retrospective study, which is usually associated with some drawbacks. Firstly, the retrospective nature of the study limits the validity of the primary estimates, and the impact of selection bias or confounding factors should not be ruled out. Secondly, study groups were not assessed during the same period of time and factors other than the study interventions might have affected the results of the analysis. Thirdly, the authors appear not to have considered the potential impact of historical trends. Another limitation of the analysis was the fact that the sample size was very small and not justified using statistical tests. Patients were identified at a single institution, which might limit the representativeness of the study sample. Thus, caution is required when extrapolating the results of the analysis to other patient populations. However, the inclusion of consecutive patients increases the robustness of the study. Details of follow-up were not reported. These issues tend to limit the internal validity of the analysis. However, it should be recognised that the objective of the study was to assess the cost and effectiveness of patients in actual treatment patterns, thus the use of an observational study was required. The use of a retrospective comparative study appears to reflect the objective of the analysis.

Validity of estimate of measure of benefit
The benefit measures used in the analysis are appropriate as QALYs and life-years capture the impact of the interventions on the most relevant dimensions of care, namely survival and quality of life. A further advantage of both measures is that they are comparable with the benefits of other health care interventions. Discounting was not applied. The approach used to derive utility weights was extensively described.

Validity of estimate of costs
The economic analysis focused on direct medical costs, which was consistent with the perspective taken in the study. Unit costs and quantities of resources used were presented separately for all items, and a detailed breakdown of items was reported, which enhances the possibility of replicating the analysis of costs in other settings. Statistical analyses of costs were carried out and extensive sensitivity analyses were performed on economic items, which strengthen the robustness of the economic estimates. The source of data was reported for all costs, and resource use reflected actual treatment patterns. This latter point represents the main strength of the study. The price year was reported, which means that reflation exercises in other time periods will be possible. Currency conversions were appropriately reported.

Other issues
The authors made extensive comparisons of their findings with those from other studies, whose results were almost homogeneous. The potential reasons for small differences across studies were provided. The other published economic evaluations were mainly based on clinical trials, while this study was based on an observational study. The issue of the generalisability of the study results to other settings was not explicitly addressed but the extensive use of sensitivity analysis enhances the external validity of the study. The analysis referred to women with advanced OC and this was reflected in the authors' conclusions. Some limitations of the analysis were highlighted by the authors and have been reported in the fields above.

Implications of the study
The study results support the use of a PC regimen for the treatment of advanced OC. The authors state that a prospective, multicentre, observational study should be carried out to corroborate the current findings.
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None stated.

Bibliographic details

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Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Aged; Aged, 80 and over; Antineoplastic Agents, Phytogenic /administration & dosage /economics; Antineoplastic Combined Chemotherapy Protocols /economics /therapeutic use; Cisplatin /administration & dosage; Cost-Benefit Analysis; Cyclophosphamide /administration & dosage; Female; Humans; Middle Aged; Ovarian Neoplasms /drug therapy /economics; Paclitaxel /administration & dosage /economics; Randomized Controlled Trials as Topic; Retrospective Studies; Treatment Outcome

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