A comparative economic analysis of pegylated liposomal doxorubicin versus topotecan in ovarian cancer in the USA and the UK


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 use of pegylated liposomal doxorubicin (PLD; Doxil/CAELYX; Sequus Pharmaceuticals Inc.) for the treatment of women with epithelial ovarian cancer that had failed first-line platinum-based chemotherapy. PLD was administered at a dose of 50 mg/m2 via a 1-hour intravenous infusion every 28 days.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women, aged 18 years or over, with measurable and assessable epithelial ovarian cancer that had recurred or failed first-line chemotherapy with a platinum-based regimen.

Setting
The setting was a hospital. The economic study was performed in sites from North America and Europe.

Dates to which data relate
The effectiveness and resource use data were collected between May 1997 and some point at the beginning of 2000. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from a published single study (Gordon et al., see Other Publications of Related Interest).

Link between effectiveness and cost data
The costing was performed on the same sample population as that used in the effectiveness analysis. An expert panel of oncologists was assembled to supplement missing data.

Study sample
Sample size calculations were performed in the planning phase of the study. These showed that a sample size of 460 patients was needed in order to assure 80% power to demonstrate clinical equivalence between PLD and topotecan, considering an assessment rate of 80%. In total, 481 patients with ovarian cancer that failed or relapsed after first-line chemotherapy with a platinum-based regimen were randomised to one of the treatment groups. The final sample
comprised 474 patients, 239 in the PLD group and 235 in the topotecan group. Seven patients were excluded because they did not receive the study drug. The authors did not provide any evidence that the study sample was representative of the study population.

**Study design**
This was a multi-centred, randomised controlled trial (RCT). A total of 104 centres participated in the study. The duration of follow-up was 1 year, or until death or disease progression. There were no losses to follow-up. The authors did not report the method of randomisation used. They also did not state whether the patients, doctors or investigators were blinded to the treatments.

**Analysis of effectiveness**
The basis of the analysis was intention to treat. The primary health outcomes assessed for each treatment arm in the clinical study were the time to disease progression or death, and the overall survival. Also assessed were health-related quality of life (HRQoL) and the number and percentage of patients experiencing adverse events associated with the treatments. HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life questionnaire (QLQ-C30). Time to progression and overall survival were estimated using Kaplan-Meier estimates and Cox regression models, adjusting for confounding factors (disease state and presence of bulky disease). Stratified analyses were performed with patients stratified on the basis of platinum sensitivity and presence of bulky disease. The authors stated that the patient groups were similar at baseline in terms of their age, disease status, platinum sensitivity, bulky disease and HRQoL.

**Effectiveness results**
The median time to disease progression or death was 113 days for PLD and 119 days for topotecan (hazard ratio, HR=1.176, 90% confidence interval, CI: 1.00 - 1.38; p=0.10).

Median overall survival was 60 weeks for PLD versus 56.7 weeks for topotecan (HR 1.12, 90% CI: 0.92 - 1.367; p=0.341).

The overall response rates (19.7% for PLD versus 17% for topotecan; p=0.390) and HRQoL were not significantly different when PLD and topotecan were compared.

The stratified analyses showed no significant difference between PLD and topotecan patients according to bulky disease. However, when comparing platinum-sensitive patients, those treated with PLD presented a significantly higher median time to progression (28.9 weeks) than those treated with topotecan (23.3 weeks), (p=0.037). They also had a significantly higher median overall survival (108 weeks versus 71.1 weeks; p=0.008).

A greater percentage of patients in the topotecan group experienced severe (grade 3) or life-threatening (grade 4) adverse events. Neutropenia was the most common adverse event among topotecan patients, with 77% topotecan versus 12% PLD patients experiencing grades 3 or 4 neutropenia. Palmar-plantar erythodysesthesia was the most common adverse event among PLD patients, with 23% of them experiencing grade 3 or 4 palmar-plantar erythodysesthesia versus 0% in the topotecan group.

**Clinical conclusions**
There were no significant differences between time to disease progression, overall response rates, overall survival and HRQoL between PLD and topotecan patients. However, a higher percentage of topotecan patients experienced severe and life-threatening adverse events due to the toxicity of the treatment. There were also significant differences in favour of PLD among platinum-sensitive patients in terms of time to progression and overall survival.

**Measure of benefits used in the economic analysis**
In general, the effectiveness results showed no significant differences between PLD and topotecan patients. Therefore,
the analysis was based on a cost-minimisation approach. Consequently, no summary measure of health benefit was used in the economic analysis.

**Direct costs**
The resource quantities and the costs were reported separately. The direct costs included in the analysis were those of the health service. The three main categories of direct costs considered were study drug, drug administration (including ambulatory visit per dose, pre-medication and specialist visits) and the treatment of adverse events. Different costs estimates were reported according to the context in which the patients were treated (i.e. USA versus UK costs), assuming that all patients were treated either in North America or Europe. Ordinary least squares models were used to predict resource use in each context. The costs were estimated from US sources (such as 2000 Medicare fees), UK sources (such as the British National Formulary, the 2000 Tariff of the National Blood Authority, and data from hospital trusts) and published studies. An expert panel of oncologists was assembled to estimate the resource use data that were lacking from the clinical trial. Therefore, the costs were derived from actual data and a guess. Some of the collected cost data were already adjusted by means of cost-to-charge ratios. The price year was 2000. Discounting was not performed. However, it does not appear to have been relevant since the patients were followed up for one year, or until death or disease progression. The study reported the average costs per patient.

**Statistical analysis of costs**
The resource use associated with each treatment was compared using t-tests. Moreover, 95% CIs were reported for the total costs.

**Indirect Costs**
The indirect costs were not reported.

**Currency**
US dollars ($). UK sterling pounds were converted to US dollars. The conversion rate was 1.0 = $1.4.

**Sensitivity analysis**
Sensitivity analyses were performed to assess the robustness of the results to different assumptions and costs. The ranges used were obtained from the panel of experts and from different sources of the cost data. Several bootstrap replications were also performed. First, considering the cost variations associated with each one of the contexts (USA and UK). Second, considering a best-case scenario for topotecan. Finally, by restricting the analyses in each context to the patients treated in that context. The areas of uncertainty investigated were, therefore, variability in the data and generalisability of the cost results.

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

**Cost results**
In the USA context, the total cost per patient was $28,220 (95% CI: 25,750 - 30,974) when treated with topotecan and $15,895 (95% CI: 14,515 - 17,306) when treated with PLD. Therefore, the cost-saving per patient treated with PLD, compared with topotecan, was $12,325 (95% CI: 9,445 - 15,415).

In the UK context, the total cost per patient was $16,906 (95% CI: 15,617 - 18,847) when treated with topotecan and $13,997 (95% CI: 12,863 - 15,392) when treated with PLD. Therefore, the cost-saving per patient treated with PLD, compared with topotecan, was $2,909 (95% CI: 779 - 3,415).

The sensitivity analyses showed that PLD always remained the least costly strategy in the USA context, although the
cost-savings varied according to the parameters considered. In the UK context, PLD turned out to be less costly in 89% of the replications when considering the best-case scenario for topotecan, and in 93% of the replications when the analysis was restricted to European patients.

Synthesis of costs and benefits
The estimated benefits and costs were not combined due to the cost-minimisation analysis undertaken.

Authors’ conclusions
Compared with topotecan, pegylated liposomal doxorubicin (PLD) presented similar clinical outcomes but different toxicity profiles. This resulted in a lower overall cost of care for patients treated with PLD.

CRD COMMENTARY - Selection of comparators
A justification was given for the comparator chosen (Gordon et al., see Other Publications of Related Interest). Topotecan was the only approved agent for recurrent ovarian carcinoma in the authors’ setting. You should decide which health technology is widely used in your own setting for the treatment of recurrent ovarian cancer.

Validity of estimate of measure of effectiveness
Although an RCT was performed, the method used to randomise the patients to the treatment arms was unclear and the doctors and patients do not appear to have been blinded. However, the study groups were shown to be comparable at analysis in terms of their baseline characteristics. The authors did not report that the study sample was representative of the study population, but it is likely that it was since a larger sample size, recruited from 104 sites, was considered for the effectiveness analysis.

Validity of estimate of measure of benefit
No summary measure of health benefit was derived since PLD and topotecan were shown to be similar in terms of clinical outcomes. Hence, a cost-minimisation analysis was undertaken.

Validity of estimate of costs
All the categories of costs relevant to the perspective adopted appear to have been included in the economic analysis. In addition, the costs related to adverse events were also considered, although the authors limited their estimation to the costs related to eight adverse events and stated that other adverse events could have occurred. The resource quantities were reported separately from the unit costs, which facilitates reflation exercises in other settings. The price year was reported. Discounting was not performed since the costs were incurred during one year.

The authors highlighted several limitations to the cost estimation. First, expert opinions were used to complete economic data, which may have underestimated the variability in the costs. Second, patients from different settings were grouped in the same dataset, which means there may be differences in resource use and costs between settings. However, sensitivity analyses investigated the impact that expert opinions and the patients’ setting had on the results obtained.

Other issues
The authors made appropriate comparisons of their results with those from other studies. Similarities in the adverse event rates were shown, although this study resulted in higher costs than another published study. The issue of the generalisability of the results to other settings was addressed. The authors commented that the setting must be considered in an economic analysis because the results obtained in one setting may not be generalisable to other settings. The study considered women with recurrent ovarian cancer and this was reflected in the authors’ conclusions.
Implications of the study
The authors stated that this was one of the first cost analyses in oncology to consider international differences in the practice of cancer care. They suggested that further research should be performed to investigate the survival advantage found for platinum-sensitive patients who receive PLD, compared with those receiving topotecan (Gordon et al., see Other Publications of Related Interest).

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Other publications of related interest


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