Role of chemotherapy for patients with recurrent platinum-resistant advanced epithelial ovarian cancer: a cost-effectiveness analysis


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 study examined several strategies for the treatment of women with recurrent platinum-resistant epithelial ovarian cancer (EOC):

- best supportive care (BSC) including hospice or palliative care;
- second-line chemotherapy monotherapy;
- second-line chemotherapy-combination therapy;
- third-line chemotherapy after disease progression on second-line monotherapy; and
- third-line chemotherapy after disease progression on second-line combination therapy.

BSC consisted of a multidiscipline approach including physicians, nurses, health care aides, and social workers to address palliative care symptoms.

In the second-line monotherapy strategy, patients received monthly liposomal doxorubicin (40 mg/m² every 4 weeks) for a total of 4 months.

In the second-line combination therapy strategy, patients received combination chemotherapy with gemcitabine (750 mg/m²) and cisplatin (30 mg/m²) on days 1 and 8 every 21 days for 4 months.

Third-line chemotherapy consisted of 3 cycles of topotecan (1.5 mg/m² per day for 5 days every 21 days).

Two separate third-line strategies were evaluated, depending on the therapy received in the second-line setting (monotherapy versus combination therapy).

Type of intervention
Treatment and palliative care.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients who had been diagnosed with advanced EOC and who subsequently underwent primary cytoreductive surgery followed by combination platinum-taxane-based chemotherapy for 6 cycles. Women experienced a recurrence of disease within 6 months of completing primary chemotherapy (platinum-resistant).
Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1996 and 2005. No dates for the resource use data were reported. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies, supplemented by authors’ opinions.

Modelling
The authors stated that a decision analysis model was constructed to assess the costs and benefits of the alternative strategies in a hypothetical cohort of 4,000 eligible women. However, no information on the model was provided.

Outcomes assessed in the review
The outcome estimated in the review was the overall survival (OS) associated with the alternative strategies. OS was defined from the time of initial recurrence. The authors combined progression-free survival with hospice care to derive the OS.

Study designs and other criteria for inclusion in the review
A review of the literature was undertaken to identify relevant studies. Data from phase III clinical trials were searched first, but most of the evidence came from phase II studies. Eight phase II studies were found for second-line monotherapy (575 patients), 2 studies for second-line combination therapy (893 patients), and 4 studies for third-line chemotherapy (624 patients). Actual doses, sample sizes and the relative risk (RR) of treatment were reported for each study.

Sources searched to identify primary studies
Not reported.

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

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

Number of primary studies included
Eighteen primary studies provided the clinical data.

Methods of combining primary studies
The primary estimates were combined by calculating simple mean values of the median OS from each study.

Investigation of differences between primary studies
Not reported.
Results of the review
The RR reduction was 13.5% with second-line monotherapy, 29.4% with second-line combination therapy and 13.2% with third-line therapy.

Median progression-free survival was 4.1 months with second-line monotherapy, 6 months with second-line combination therapy and 3 months with third-line therapy (extra progression-free survival with respect to second-line therapy).

When additional months in hospice care were considered, the OS from the initial recurrence (after first-line therapy) was estimated to be 6 months with second-line monotherapy, 8 months with both second-line combination therapy and third-line previous monotherapy, and 10 months with third-line previous combination.

Methods used to derive estimates of effectiveness
As the authors were unable to find published evidence of the OS for the BSC strategy, they made an assumption based on clinical experience.

Estimates of effectiveness and key assumptions
The OS for the BSC strategy was assumed to be 3 months.

Measure of benefits used in the economic analysis
The summary benefit measure used was OS. This was estimated from the review of the literature review.

Direct costs
The analysis of the costs was performed from the perspective of the third-party payer. It included the direct medical costs associated with the five strategies. For example, BSC included outpatient office visits, emergency department visits, hospitalisations and home health care, as well as medications and other palliative supportive interventions such as blood transfusions, home oxygen and intravenous hydration. The costs of treating chemotherapy-related toxicity and complications were not considered. Accordingly, the use of erythropoietic agents for palliative intent in the BSC strategy was not included.

The unit costs were not presented separately from the quantities of resources used. The source of the data on resource consumption was not explicitly reported. The costs were based on local charges adjusted using a cost-to-charge ratio of 60%. The pharmacy costs were estimated from average wholesale prices, while laboratory and procedural estimates were obtained from the University of Alabama. Discounting was not relevant as the costs were incurred during a short timeframe. The price year was 2004.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
A univariate sensitivity analysis was carried out to assess the robustness of the cost-effectiveness estimates to variations.
in the baseline OS rates and costs. The parameters investigated were varied across reasonable ranges that were set by the authors.

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

**Cost results**
The expected costs associated with the treatment of a hypothetical cohort of 4,000 patients were:

- $49 million with BSC,
- $113 million with second-line monotherapy,
- $314 million with second-line combination therapy,
- $316 million with third-line chemotherapy with previous second-line monotherapy, and
- $517 million with third-line chemotherapy with previous second-line combination therapy.

**Synthesis of costs and benefits**
Average and incremental cost-effectiveness ratios were calculated in order to combine the costs and benefits of the alternative strategies.

The average cost per month of OS was:

- $4,065 with BSC,
- $4,703 with second-line monotherapy,
- $9,826 with second-line combination therapy,
- $9,861 with third-line chemotherapy with previous monotherapy, and
- $12,927 with third-line chemotherapy with previous combination therapy.

The incremental analysis showed that the incremental cost per life-year gained with second-line monotherapy over BSC was $64,104.

The incremental cost-effectiveness ratios of the other strategies (with respect to the next most effective strategy) were far above $100,000 per life-year gained. For example, the incremental cost per month of OS was $302,316 for second-line combination therapy over monotherapy and $303,984 for third-line chemotherapy over second-line combination therapy.

The univariate sensitivity analysis suggested that the OS with chemotherapy strategies would have to improve, or the costs of chemotherapy would have to decrease, for these strategies to be cost-effective. For example, using a threshold of $50,000 per life-year gained, the OS of second-line monotherapy would have to be 7 months (6 months in the base-case analysis) for the intervention to be cost-effective. Similarly, the cost of second-line monotherapy would have to fall below $16,500 ($20,960 per patient in the base-case) for this therapy to be cost-effective.

**Authors’ conclusions**
Best supportive care (BSC) was the most cost-effective option for women with recurrent platinum-resistant epithelial ovarian cancer (EOC). Second-line monotherapy was a reasonable alternative strategy with a cost per life-year gained of
CRD COMMENTARY - Selection of comparators
The authors provided a clear justification for the choice of the comparators considered in the study. They stated that the most commonly used chemotherapy agents were chosen. The interventions examined were described and dosages and frequency of administration were given. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness estimates were based on a review of the literature. However, neither the conduct nor the methods used were described, and the authors did not state which sources were searched. The inclusion of many phase II studies casts some doubts on the validity of the primary estimates, although it was stated that no phase III studies were available. The authors reported some information on each primary study (e.g., dosages, number of patients involved and main clinical results), but the issue of heterogeneity across the primary estimates was not addressed and a non-weighted average of the clinical results of these studies was calculated in order to populate the decision model. The authors made a key assumption on the clinical benefit of BSC. The use of sensitivity analyses enhances the robustness of the analysis.

Validity of estimate of measure of benefit
OS was an appropriate benefit measure because it reflects the main dimension of health for women with EOC. Discounting was not relevant due to the poor survival of these patients. Life-years can be compared with the benefits of other health care interventions.

Validity of estimate of costs
The cost categories evaluated were consistent with the perspective adopted. The costs were listed but a detailed breakdown of cost items was not provided. Further, the costs were often presented as macro-categories, thus details of the unit costs and quantities of resources used were not provided. This could limit the possibility of replicating the analysis in other settings. Local charges were adjusted using a cost-to-charge ratio, but this is not always appropriate from the perspective of a third-party payer since the charge may be the cost to the payer. The cost estimates were treated deterministically and only the total costs were varied in the sensitivity analysis. In effect, the impact of individual cost items on the total costs was not evaluated. The price year was reported, which will facilitate reflation exercises in other settings. The authors pointed out that their cost analysis was conservative since some of the additional costs associated with chemotherapy strategies were not taken into consideration.

Other issues
The authors did not compare their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. However, it was stated that there was a lack of published cost-effectiveness analyses for the strategies compared. The use of sensitivity analysis will have gone some way to improving the external validity of the analysis, although only a few items were varied. The study referred to women with recurrent platinum-resistant EOC and this was reflected in the authors’ conclusions.

Implications of the study
The study results did not support the use of chemotherapy in women with recurrent platinum-resistant EOC. The authors noted that the results of the current analysis suggest that more effective treatments for recurrent ovarian cancer should be developed.

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Other publications of related interest
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