

Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation

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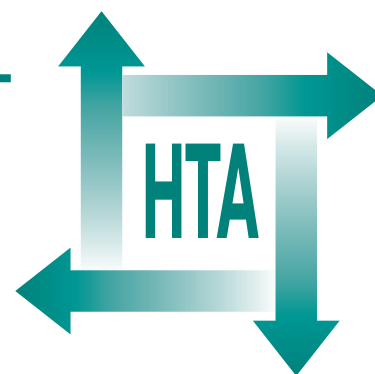
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Executive summary

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Executive summary

Background

Ovarian cancer is the most common gynaecological cancer, with an annual incidence of 21.9 per 100,000 women in England and 26.7 per 100,000 in Wales (2000 figures). The prognosis is generally poor, owing to the advanced stage of disease at detection in most cases, and the UK 5-year survival rate is only around 30%. The current guidance issued by the National Institute for Health and Clinical Excellence is that first-line chemotherapy should include either paclitaxel in combination with a platinum-based chemotherapy regimen, or a platinum-based regimen alone (carboplatin or cisplatin). As the majority of patients ultimately relapse and require treatment with second-line therapy, the guidance is that patients who have received recommended first-line therapy should not be treated with the same agents. Pegylated liposomal doxorubicin hydrochloride (PLDH), topotecan and paclitaxel may therefore be considered alongside other drugs licensed for second-line therapy in advanced ovarian cancer. Participants who had not received paclitaxel as a component of first-line therapy may receive it as second-line.

Objectives of the review

The objectives were to examine the clinical effectiveness and cost-effectiveness of intravenous formulations of topotecan monotherapy, PLDH monotherapy and paclitaxel used alone or in combination with a platinum-based compound for the second-line or subsequent treatment of advanced ovarian cancer.

Methods

Search strategy

Seventeen databases were searched for randomised controlled trials (RCTs) and systematic reviews for the clinical effectiveness of PLDH, topotecan and paclitaxel and economic evaluations of the cost-effectiveness of PLDH, topotecan and paclitaxel. Previous searches were conducted up to 2000. The current searches were therefore limited to publication years 2000–4.

Inclusion/exclusion criteria

Two reviewers independently screened all titles and/or abstracts including economic evaluations. The full text of any study judged to be relevant by

either reviewer was obtained and assessed for inclusion or exclusion. Disagreements were resolved through discussion. For the assessment of clinical effectiveness, RCTs that compared topotecan monotherapy, PLDH monotherapy or paclitaxel administered alone or in combination with a platinum-based compound with any other comparator including usual supportive care were included. For the assessment of cost-effectiveness, a broader range of studies was considered.

Data extraction and quality assessment

Data from included studies were extracted by one reviewer and independently checked for accuracy by a second reviewer. Individual studies were assessed for quality by one reviewer and independently checked for accuracy by a second.

Methods of analysis/synthesis

The results of the data extraction and quality assessment of the RCTs were presented in structured tables and as a narrative summary. For the cost-effectiveness section of the report, details of each identified published economic evaluation, together with a critical appraisal of its quality, were presented in structured tables.

Handling company submissions

All the clinical effectiveness data included in the company submissions from Bristol Myers Squibb, GlaxoSmithKline and Schering-Plough Ltd were assessed. Where this met the inclusion criteria it was included in the clinical effectiveness review. All economic evaluations (including accompanying models) included in the company submissions were assessed and a detailed assessment of the assumptions underlying the submitted analyses was undertaken. A new model was developed to assess the costs of the alternative treatments, the differential mean survival duration and the impact of health-related quality of life. Monte-Carlo simulation was used to reflect uncertainty in the cost-effectiveness results.

Results

A total of 2542 titles and abstracts were screened for inclusion in the review of clinical and cost-effectiveness; 194 studies were ordered as full papers and assessed in detail. Nine RCTs were identified. In five of these trials, both the



comparators were used within their licensed indications. Of these five trials, three of the trials included participants with both platinum-resistant and platinum-sensitive advanced ovarian cancer, and a further two trials only included participants with platinum-sensitive disease. The comparators that were assessed in the three trials that included both subtypes of participants were PLDH versus topotecan, topotecan versus paclitaxel and PLDH versus paclitaxel. In the further two trials that included participants with the subtype of platinum-sensitive disease, the comparators that were assessed were single-agent paclitaxel versus a combination of cyclophosphamide, doxorubicin and cisplatin (CAP) and paclitaxel plus platinum-based chemotherapy versus conventional platinum-based therapy alone.

A further four trials were identified and included in the review in which one of the comparators in the trial was used outside its licensed indication. The comparators assessed in these trials were oxaliplatin versus paclitaxel, paclitaxel given weekly versus every 3 weeks, paclitaxel at two different dose levels and oral versus intravenous topotecan.

Clinical effectiveness

Trials including participants with refractory, resistant and platinum-sensitive disease

PLDH versus topotecan

PLDH was marginally more effective than topotecan in terms of overall survival in the total trial population that included both participants with platinum-sensitive and platinum-resistant disease. However, this result appears to be driven by the more highly significant benefit of PLDH treatment in the platinum-sensitive subgroup of participants. For participants with platinum-resistant disease there was no statistically significant difference in overall survival between the PLDH and topotecan treatment groups. There were also no statistically significant differences between the PLDH and topotecan groups in terms of progression-free survival, response or quality of life.

In terms of toxicities reported during the trial, the rates of grade 3 stomatitis, palmar-plantar erythrodysesthesia (PPE), mucous membrane disorder and rash were significantly higher in the PLDH treatment arm. In the topotecan arm the rates of grade 3 and 4 haematological toxicities and grade 3 alopecia and fever were significantly higher.

Topotecan versus paclitaxel

There were no statistically significant differences between the two treatment groups in terms of overall survival, time to progression, response rate

or response duration. The point estimates for all of these outcomes favoured treatment with topotecan over paclitaxel. However, there was a significant difference between the two treatment groups in terms of time to response, favouring paclitaxel.

In this trial, treatment with topotecan was associated with significantly more grade 3 and 4 haematological toxicities compared with paclitaxel. In addition, grades 3 and 4 nausea, vomiting, constipation, abdominal pain, asthenia, fatigue and fever/infection were significantly higher in this group. Treatment with paclitaxel was associated with significantly more grade 3 and 4 alopecia, arthralgia, myalgia and skeletal pain compared with the topotecan treatment arm.

PLDH versus paclitaxel

In relation to overall survival, there was no significant difference between the PLDH and paclitaxel treatment groups. Treatment with PLDH was associated with significantly more grade 3 PPE, ascites, stomatitis and dyspnoea compared with treatment with paclitaxel. Treatment with paclitaxel was associated only with a higher incidence of grade 3 alopecia relative to PLDH. This trial was terminated prematurely, therefore the results should be interpreted with caution.

Trials including participants with platinum-sensitive disease only

Paclitaxel versus CAP

CAP was more effective than paclitaxel in terms of both overall and progression-free survival. There were no significant differences between the two treatment regimens in terms of response. However, the incidence of grade 3 and 4 haematological toxicities and grade 2 nausea and vomiting was significantly higher in the CAP treatment arm. Treatment with paclitaxel was associated with significantly higher rates of alopecia and allergic reactions relative to treatment with CAP.

Paclitaxel in combination with platinum-based chemotherapy versus platinum-based therapy alone

Paclitaxel in combination with platinum-based chemotherapy was more effective than platinum monotherapy in relation to both overall survival and progression-free survival. However, there was no significant treatment benefit observed for combination therapy for response rates or overall quality of life.

Treatment with paclitaxel in combination with platinum was associated with significantly higher rates of grades 2–4 neurological toxicity and alopecia. Treatment with platinum monotherapy was associated with significantly higher rates of haematological toxicity. ►

Trials in which one of the comparators was used outside the licensed indication

Paclitaxel versus oxaliplatin

There were no statistically significant differences between the paclitaxel and oxaliplatin treatment groups in terms of overall survival, time to progression, response rate, response duration or quality of life. Treatment with paclitaxel was associated with a higher incidence of severe neutropenia, whereas oxaliplatin was associated with higher rates of thrombocytopenia.

Paclitaxel given weekly versus every 3 weeks

There was no significant treatment benefit for either of these regimens as assessed by overall survival, time to progression, response or response duration. Treatment with paclitaxel every 3 weeks was associated with a significantly higher incidence of grade 3 and 4 neutropenia and alopecia, whereas treatment every week was associated with problems with nail changes.

Paclitaxel 175 versus 250 mg/m²

There were no statistically significant differences between participants treated with the lower dose regimen and those treated with the higher dose regimen for overall survival or progression-free survival. There was a significant benefit in favour of the higher dose regimen for response rates. However, the reporting of grade 3 and 4 haematological toxicities was more common in the higher dose treatment group.

Oral versus intravenous topotecan

There was a significant benefit in favour of intravenous topotecan for overall survival. However, no further significant difference between the two treatment regimens was found for time to progression, response rate, response duration and time to response. Neutropenia and leucopenia occurred frequently in both treatment groups, but were higher in the intravenous treatment group. The rates of grade 3 and 4 nausea, vomiting, diarrhoea and fever were all significantly higher in the oral treatment regimen group compared with the intravenous treatment arm.

Cost-effectiveness

Four studies met the inclusion criteria for the cost-effectiveness review. In addition, separate submissions were received from Bristol Myers Squibb, GlaxoSmithKline and Schering-Plough Ltd. The review of the economic evidence from the literature and industry submissions identified a number of significant limitations in existing studies assessing the cost-effectiveness of PLDH, topotecan and paclitaxel. A new model was developed to address the limitations identified in these sources and to provide a direct comparison of the full range of possible strategies that are relevant to the NHS. The model explored a range

of uncertainties and sources of variability that were not fully addressed in existing data sources. Two separate analyses (Analysis 1 and Analysis 2) were required in order to reflect the heterogeneity identified in the different trials and the difficulties encountered in obtaining robust estimates using a consistent approach for the methods of evidence synthesis of the relative treatment effects.

Analysis 1 assessed the cost-effectiveness of PLDH, topotecan and paclitaxel administered as monotherapies. Sensitivity analysis was undertaken to explore the impact of patient heterogeneity (e.g. platinum-sensitive and platinum-resistant/refractory patients), the inclusion of additional trial data (30-57) and alternative assumptions regarding treatment and monitoring costs. In the base-case results for Analysis 1, paclitaxel monotherapy emerged as the cheapest treatment. When the incremental cost-effectiveness ratios (ICERs) were estimated, topotecan was dominated by PLDH. Hence the options considered in the estimation of the ICERs were paclitaxel and PLDH. The ICER for PLDH compared with paclitaxel was £7033 per quality-adjusted life-year (QALY) in the overall patient population (comprising platinum-sensitive, -refractory and -resistant patients). The ICER was more favourable in the platinum-sensitive group (£5777 per QALY) and less favourable in the platinum-refractory/resistant group (£9555 per QALY). The cost-effectiveness results for the base-case analysis were sensitive to the inclusion of trial 30-57. Incorporating the results of trial 30-57 resulted in less favourable estimates for the ICER for PLDH versus paclitaxel compared with the base-case results. The ICER of PLDH compared with paclitaxel was £20,620 per QALY in the overall patient population, £16,183 per QALY in the platinum-sensitive population and £26,867 per QALY in the platinum-resistant and -refractory population.

The results from Analysis 2 explored the cost-effectiveness of the full range of treatment comparators for platinum-sensitive patients. The treatment options considered in this model comprised PLDH, topotecan, paclitaxel-monotherapy, CAP, paclitaxel/platinum combination therapy and platinum monotherapy. Owing to the less robust approaches that were employed to synthesise the available evidence and the heterogeneity between the different trials, the reliability of these results should be interpreted with some caution. Topotecan, paclitaxel monotherapy and PLDH were all dominated by platinum monotherapy (i.e. higher costs and lower QALYs). After excluding these alternatives, the treatments that remained under consideration were platinum monotherapy, CAP and paclitaxel-

platinum combination therapy. Of these three alternatives, platinum monotherapy was the least costly and least effective. The ICER for CAP compared with platinum monotherapy was £16,421 per QALY. The ICER for paclitaxel–platinum combination therapy compared with CAP was £20,950 per QALY.

Conclusions

Clinical effectiveness

Participants with platinum-resistant disease

For participants with platinum-resistant disease there was a low probability of response to treatment with PLDH, topotecan or paclitaxel. Furthermore, there was little difference between the three comparators in relation to overall survival. The comparators did, however, differ considerably in their toxicity profiles. Given the low survival times and response rates, it appears that the maintenance of quality of life and the control of symptoms and toxicity are paramount in this patient group. As the three comparators differed significantly in terms of their toxicity profiles, patient and physician choice is also an important element that should be addressed when decisions are made regarding second-line therapy. It can also be suggested that this group of patients may benefit from being included in further clinical trials of new drugs.

Participants with platinum-sensitive disease

For participants with platinum-sensitive disease there was a considerable range of median survival times observed across the trials. The most favourable survival times and response rates were observed for paclitaxel and platinum combination therapy. This suggests that treatment with combination therapy may be more beneficial than treatment with a single-agent chemotherapeutic regimen. In terms of single-agent compounds, the evidence suggests that PLDH is more effective than topotecan. Evidence from a further trial that compared PLDH and paclitaxel suggests that there is no significant difference between these two comparators in this trial. The three comparators did, however, differ significantly in terms of their toxicity profiles across the trials. Although treatment with PLDH may therefore be more beneficial than that with topotecan, patient and physician choice as to the potential toxicities associated with each of the comparators and the patient's ability and willingness to tolerate these are of importance.

Cost-effectiveness

The following conclusions are possible assuming the NHS is willing to pay up to £20,000–40,000 per additional QALY:

- PLDH appears to be cost-effective compared with topotecan and paclitaxel monotherapy, in terms of the overall patient population and the main subgroups considered.
- The cost-effectiveness results for the base-case analysis were sensitive to the inclusion of trial 30-57. Incorporating the results of trial 30-57 gave less favourable estimates for the ICER for PLDH versus paclitaxel monotherapy, compared with the base-case results. Although the ICER of PLDH compared with paclitaxel monotherapy was less favourable, PLDH was still cost-effective compared with topotecan and paclitaxel monotherapy.
- For platinum-sensitive patients, the combination of paclitaxel and platinum appears to be cost-effective.

Research recommendations

Participants with platinum-resistant disease

On the strength of the evidence reviewed in this assessment, it can be suggested that participants with platinum-resistant disease may benefit from being included in further clinical trials of new drugs.

Participants with platinum-sensitive disease

To assess the effectiveness of combination therapy against a single-agent non-platinum based compound, it can be suggested that a trial that compared paclitaxel in combination with a platinum-based therapy versus single-agent PLDH would be a reasonable option.

Publication

Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al.* Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation. *Health Technol Assess* 2006;**10**(9).

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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