Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for advanced recurrent or refractory ovarian cancer: a systematic review and economic evaluation

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Scientific summary

Treatment for advanced recurrent or refractory ovarian cancer

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Background

Ovarian cancer is the fifth most common cancer in the UK, and the fourth most common cause of cancer death. It has been estimated that the lifetime risk (adjusting for multiple primaries) of developing ovarian cancer is 1 in 54 for women in the UK (based on data from 2008). Ovarian cancer is predominantly a disease of older, postmenopausal women, with > 80% of cases diagnosed in people of > 50 years of age. Treatments for newly diagnosed ovarian cancer are given with curative intent, and typically involve a combination of cytoreductive surgery and chemotherapy. Response to first-line treatment is achieved in approximately 70–80% of patients. However, some people do not respond to treatment and, of those who do respond, between 55% and 75% will relapse within 2 years of completing treatment. In addition, some people develop an allergy to, or cannot tolerate, treatment with platinum-derived agents.

A person's response to first-line platinum-based therapy is indicative of their response to second and subsequent lines of platinum-based treatment, with the length of the platinum-free interval (PFI) and the extent of relapse (site and number of tumours) particularly prognostic of response. For people for whom further treatment with a platinum-based regimen is appropriate, the choice of treatment has long been based on PFI, i.e. the period of time between the last treatment of one regimen and the first treatment of the next regimen. People who relapse at 6 months or more after completion of platinum-based chemotherapy are categorised as having platinum-sensitive disease, with further subdivision into partially platinum sensitive (relapse at 6–12 months after initial chemotherapy) or fully platinum sensitive (relapse at ≥ 12 months after initial chemotherapy). People who relapse within 6 months of completion of platinum-based chemotherapy are classed as platinum resistant, and those who do not respond to platinum-based chemotherapy are platinum refractory. At this time, it is uncertain which chemotherapy regimen is more clinically effective and cost-effective for the treatment of advanced ovarian cancer that has recurred after, or is refractory to, treatment with further platinum-based regimens.

Objectives

The aim of the project was to determine the comparative clinical effectiveness and cost-effectiveness of topotecan (Hycamtin®, GlaxoSmithKline), pegylated liposomal doxorubicin hydrochloride (PLDH; Caelyx®, Schering-Plough), paclitaxel (Taxol®, Bristol-Myers Squibb), trabectedin (Yondelis®, PharmaMar) and gemcitabine (Gemzar®, Eli Lilly and Company) for treatment of advanced ovarian cancer that recurs after or is refractory to treatment with a platinum-based regimen, and for the treatment of those who are allergic to or cannot tolerate platinum-derived agents.

Methods

Electronic databases (MEDLINE®, EMBASE, Cochrane Central Register of Controlled Trials, Health Technology Assessment database and NHS Economic Evaluations Database) and trial registries were searched from inception to May 2013. Additionally, submissions from manufacturers were reviewed. Double-blind, randomised, placebo-controlled trials and economic evaluations were included, based on prespecified inclusion criteria. Two reviewers independently applied inclusion and exclusion criteria. Data from included studies were extracted into a standardised data extraction form by one reviewer and validated by a second. Quality of included studies was assessed independently by two reviewers using standard checklists. Extracted data and quality assessment for each study were presented in structured tables and as a narrative summary. Where sufficient comparable data were available for each outcome

measure, network meta-analyses (NMAs) were performed using a Bayesian Markov chain Monte Carlo simulation. Evidence was considered for the clinical outcomes of overall survival (OS); progression-free survival (PFS); overall response rate; health-related quality of life (HRQoL); and adverse effects of treatment. Treatment effects were analysed as hazard ratios (HRs) for time to event outcomes and as odds ratios for dichotomous data.

A de novo economic model was developed to assess the impact of various factors on incremental costs per quality-adjusted life-year (QALY) gained. The model developed was a semi-Markov cohort model with three health states: progression-free disease; progressed disease; and death. Estimates of PFS and OS were obtained from the NMA of clinical effectiveness data. Utilities were obtained from a systematic review of the quality of life (QoL) literature. Costs were obtained from standard UK sources. Probabilistic, one-way and scenario analyses were carried out to assess parameter uncertainty.

Results

The systematic review of the clinical effectiveness literature identified 7642 potentially relevant studies, of which 1649 were found to be duplicate references. Of the remaining 5993 studies, 5889 were excluded at abstract appraisal. Evaluation of the full publication of 104 studies identified 16 randomised controlled trials (RCTs) (28 publications) of relevance to the review of clinical effectiveness. Of the 16 RCTs identified (5368 people), five evaluated the intervention and comparator within their licensed indication, and dose and route of administration. The remaining 11 RCTs evaluated the intervention or comparator outside the parameters specified in the licence, in terms of, for example, dose or route of administration. A single RCT was identified for most comparisons, which precluded evaluation by standard pairwise meta-analysis. No RCT identified evaluated interventions specifically in people who were allergic or intolerant to platinum-based treatments. Clinical expert opinion is that regimens not containing platinum are likely to be of similar effectiveness in those who have an allergy or are intolerant to platinum and in those who are able to receive further platinum-based treatment.

From the cost-effectiveness systematic review, 21 economic evaluations related to recurrent ovarian cancer were identified. No single cost-effectiveness analysis considering the full range of interventions and comparators relevant for this assessment was identified. Of the 21 studies, 13 were cost–utility analyses. Most of the published UK evidence evaluated the cost-effectiveness of treatments in recurrent ovarian cancer based upon the model developed for an earlier review. This model comprised three health states: stable disease; progressive disease; and death.

Results from head-to-head comparative RCTs were in agreement with the results from the NMA for the same comparison. Based on expert opinion, it had been prespecified that analyses would focus on the subgroups of people with platinum-sensitive and platinum-resistant/-refractory (PRR) disease. Of those RCTs carrying out analyses based on PFI, all RCTs reported PFI as a categorical variable. In one RCT, evaluating trabectedin plus PLDH compared with PLDH monotherapy, after retrospective identification of an imbalance in PFI at baseline between the two treatment groups, data were analysed controlling for PFI as a continuous variable. Analysis of PFI as a continuous variable resulted in a shift from a non-statistically significant to a statistically significant gain in OS favouring trabectedin plus PLDH. As no other RCT evaluated PFI as a continuous variable, for consistency, the decision was taken to use estimates of effect from this trial, based on PFI as a categorical variable.

For the subgroup of people with platinum-sensitive recurrent ovarian cancer, it was possible to construct two networks for most clinical outcomes: one network evaluating platinum-based regimens and one evaluating non-platinum-based regimens. For the outcome OS, of the combination platinum-based treatments compared with platinum monotherapy, significant gains in OS were observed for PLDH

plus platinum and paclitaxel plus platinum, but not for gemcitabine plus carboplatin compared with platinum monotherapy:

- Pegylated liposomal doxorubicin hydrochloride plus platinum compared with platinum monotherapy: HR 1.267, 95% credible interval (CrI) 1.030 to 1.545 (HR of > 1 favours PLDH plus platinum).
- Paclitaxel plus platinum compared with platinum monotherapy: HR 1.290, 95% CrI 1.096 to 1.509 (HR of > 1 favours paclitaxel plus platinum).
- Gemcitabine plus carboplatin compared with platinum monotherapy: HR 1.051, 95% CrI 0.815 to 1.335 (HR of > 1 favours gemcitabine plus carboplatin).
- For PFS, PLDH plus platinum significantly prolonged PFS compared with paclitaxel plus platinum: HR 0.817, 95% CrI 0.717 to 0.927 (HR of < 1 favours PLDH plus platinum).

Of the non-platinum-based treatments, results from the NMA indicated that PLDH monotherapy and trabectedin plus PLDH significantly prolong OS, but not PFS, compared with topotecan monotherapy. There was no statistically significant difference in OS or PFS between topotecan monotherapy and paclitaxel monotherapy.

Overall survival (hazard ratio of < 1 favours topotecan)

- Pegylated liposomal doxorubicin hydrochloride monotherapy compared with topotecan monotherapy: HR 1.367, 95% CrI 1.035 to 1.770.
- Trabectedin plus PLDH compared with topotecan monotherapy: HR 1.658, 95% CrI 1.157 to 2.307.
- Paclitaxel monotherapy compared with topotecan monotherapy: HR 1.145, 95% CrI 0.808 to 1.576.

Progression-free survival (hazard ratio of < 1 favours topotecan)

- Pegylated liposomal doxorubicin hydrochloride monotherapy compared with topotecan monotherapy: HR 1.298, 95% CrI 0.979 to 1.688.
- Trabectedin plus PLDH compared with topotecan monotherapy: HR 1.797, 95% CrI 1.207 to 2.578.
- Paclitaxel monotherapy compared with topotecan monotherapy: HR 0.842, 95% CrI 0.539 to 1.262.

In people with PRR disease, treatments evaluated were PLDH monotherapy, paclitaxel monotherapy, topotecan monotherapy given every 3 weeks (conventional regimen), and topotecan monotherapy given weekly. No statistically significant difference was found between any treatment regimens in either OS or PFS.

Of the 16 RCTs identified, 10 reported data on QoL. The reporting of QoL was minimal in most studies, with the majority of studies presenting a narrative description of changes in QoL rather than absolute changes in QoL score. A systematic review of HRQoL reporting in ovarian cancer trials recognised considerable disparity in the level of reporting of QoL results, the questionnaires used to evaluate QoL, and the time points for evaluation. Given the often palliative nature of second- and subsequent-line chemotherapeutic treatments for ovarian cancer, there has been a move to place greater emphasis on assessment of QoL in this condition.

Adverse effects reported by individual studies were typically as would be expected for the individual treatments based on the Summary of Product Characteristics. Commonly occurring adverse effects were alopecia, nausea and vomiting, haematological toxicities (neutropenia, anaemia, thrombocytopenia and leucopenia). Based on expert clinical advice, the NMA was restricted to adverse effects that were considered to be most problematic for patients or most likely to consume substantial health-care resource, focusing on severe (grades 3 and 4) effects: allergic reaction; alopecia; anaemia; fatigue; febrile neutropenia; nausea and vomiting; and neuropathy. However, a NMA was not possible for many adverse effects because of a lack of data. Overall, no chemotherapy was consistently associated with either a lower risk or a higher risk of the severe adverse events assessed.

Cost-effectiveness analysis indicated that, for people with platinum-sensitive disease and receiving platinum-based therapy, the estimated probabilistic incremental cost-effectiveness ratio (ICER; incremental cost per additional QALY) for paclitaxel plus platinum compared with platinum was £24,539. The probability of paclitaxel plus platinum being considered cost-effective at a threshold of £30,000 per additional QALY was estimated to be 78%. Gemcitabine plus carboplatin was extendedly dominated. In addition, PLDH plus platinum was strictly dominated; however, the total costs and QALYs associated with PLDH plus platinum and paclitaxel plus platinum were similar. The base-case probabilistic ICER for the addition of PLDH to platinum therapy was estimated to be £30,188 and the probability of PLDH plus platinum being considered cost-effective compared with platinum therapy was estimated to be 48%, at a threshold of £30,000 per additional QALY. For people with platinum-sensitive disease and receiving non-platinum-based therapy, the probabilistic ICERs associated with PLDH compared with paclitaxel, and trabectedin plus PLDH compared with PLDH, were estimated to be £25,931 and £81,353, respectively. PLDH was associated with a 59% probability of being considered cost-effective compared with paclitaxel at a threshold of £30,000 per additional QALY. Trabectedin plus PLDH was associated with a 0% probability of being considered cost-effective compared with PLDH at a threshold of £30,000. Topotecan was strictly dominated. For people with PRR disease, the probabilistic ICER associated with topotecan compared with PLDH was estimated to be £324,188, with a 0% probability of being considered cost-effective compared with PLDH at a threshold of £30,000 per additional QALY. Paclitaxel was strictly dominated. All estimates of cost-effectiveness were highly sensitive to the estimates of OS used to inform the economic model.

Limitations

A single RCT was identified for most comparisons evaluated in the clinical effectiveness review. The sparse number of identified trials necessitated use of a fixed-effects model for the NMA. In addition, the 'linear' nature of the networks constructed for the NMA prevented exploration of potential inconsistency in each analysis. The lack of data to facilitate construction of a single network encompassing platinum- and non-platinum-based regimens in people with platinum-sensitive disease means that conclusions cannot be drawn on the comparative clinical effectiveness and cost-effectiveness of these treatments in this subgroup.

In addition, unadjusted HRs for PFS and OS were used within the clinical effectiveness and cost-effectiveness analysis. Adjusting for baseline characteristics, in particular PFI, might be important because certain characteristics are considered to influence prognosis. Adjusted HRs were available for a small number of comparisons. In the absence of an adjusted dataset for all comparisons, it was considered appropriate to analyse unadjusted HRs.

Conclusions

For people with platinum-sensitive disease who receive treatment with platinum-based therapies, paclitaxel plus platinum could be considered cost-effective compared with platinum at a threshold of £30,000 per additional QALY. For people with platinum-sensitive disease and treated with non-platinum-based therapies, it is unclear whether PLDH would be considered cost-effective compared with paclitaxel at a threshold of £30,000 per additional QALY; trabectedin plus PLDH is unlikely to be considered cost-effective compared with PLDH. For PRR patients, it is unlikely that topotecan would be considered cost-effective compared with PLDH.

Research implications

No RCT was identified evaluating the effects of treatments in people who are allergic to, or cannot tolerate, platinum-derived agents. A RCT in this population and evaluating currently recommended treatments could provide an evidence base to underscore current guidance.

In people with platinum-sensitive ovarian cancer, it was not possible to compare platinum-based regimens with non-platinum-based regimens. A RCT comparing platinum-based with non-platinum-based treatments might help to verify the comparative effectiveness of these regimens.

Given the palliative nature of second-line or later treatment for recurrent ovarian cancer, and the limited data available on QoL, particularly for patients with PRR disease, research to determine reliable estimates of QoL in recurrent advanced ovarian cancer might be warranted.

Platinum-free interval has been established as an important prognostic factor. Further research evaluating the appropriateness of evaluating PFI as a continuous variable compared with a categorical variable might be warranted.

Limited information on best supportive care was identified. Some people may choose to not receive further treatment, and research into what constitutes best supportive care, and the impact of best supportive care on QoL, might help to inform the decision-making process from the perspective of both the clinician and the person with advanced ovarian cancer.

Study registration

This study is registered as PROSPERO CRD42013003555.

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