Rapid review

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer

C Forbes*
L Shirran
A-M Bagnall
S Duffy
G ter Riet

NHS Centre for Reviews and Dissemination, University of York, UK

* Corresponding author

Topotecan for ovarian cancer

Executive summary

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Executive summary

Background

Ovarian cancer is the most common gynaecological cancer with an annual incidence of 21.6 per 100,000 in England and Wales. Due to the often asymptomatic nature of the early stages of the disease, most cases are not detected until the advanced stages. Consequently, the prognosis after diagnosis is poor and the 5-year survival rate in the UK is only about 30%. Current recommendations suggest that first-line chemotherapy for ovarian cancer should involve paclitaxel and platinum (Pt)-based therapy (cisplatin/carboplatin), however, most patients develop resistant or refractory disease and require second-line therapy. Patients may respond to re-challenge with Pt-agents if the treatment-free interval is > 6 months, but an alternative is often required. Topotecan is one of six drugs currently licensed in the UK for second-line therapy, and recent reviews suggest that it has modest efficacy in the treatment of advanced disease and performs favourably against paclitaxel. However, these reviews are based on a limited number of reports mainly consisting of non-randomised Phase I and II studies.

Objectives of the review

To examine the clinical effectiveness and cost-effectiveness of oral and intravenous topotecan (Hycamtin®, SmithKline Beecham, UK) for the treatment of all stages of ovarian cancer.

Methods

Search strategy

Sixteen electronic databases from inception to September 2000 and Internet resources were searched, in addition to the bibliographies of retrieved articles and submissions from pharmaceutical companies.

Inclusion and exclusion criteria

Two reviewers independently screened all titles/abstracts and included/excluded studies based on full copies of manuscripts. Any disagreements were resolved through discussion. Only randomised controlled trials (RCTs) and full economic evaluations comparing topotecan to non-topotecan regimens were included. All stages of therapy and disease were considered, and the outcomes included were survival, response, symptom relief, quality of life, adverse effects and costs.

Data extraction strategy

Data were extracted into an Access database by one reviewer and checked by a second. Any disagreements were resolved through discussion.

Quality assessment strategy

Two reviewers, using specified criteria, independently assessed the quality of the clinical effectiveness studies and the economic evaluations. Any disagreements were resolved through discussion.

Analysis strategy

Due to the limited number of studies included in the review and the fact that they compared topotecan with different comparators, the outcome data could not be pooled statistically. Clinical effectiveness data are discussed separately under the different outcome subheadings. For time-to-event data, hazard ratios with 95% confidence intervals are presented where available, and for the remaining outcomes, relative risks are reported or calculated where sufficient data were available. Relative risk data are also presented in the form of Forest plots without pooled estimates. Economic data are presented in the form of a summary and critique of the evidence, and a grading (A–I) assigned to each study indicating the direction and magnitude of the cost-effectiveness data.

Results

Included studies

A total of 568 titles/abstracts were identified and screened for relevance. Full copies of 72 papers were assessed and seven published manuscripts reporting details of two studies of clinical effectiveness and one economic evaluation were included. Further details of the two clinical effectiveness studies and two new economic evaluations were identified from confidential company sub-

missions. Overall, two international multicentre RCTs of effectiveness comparing topotecan with paclitaxel (trial 039) and topotecan with caelyx (trial 30-49) were included in the review. The three economic evaluations included in the review comprised one cost-minimisation analysis (CMA) comparing topotecan with caelyx, one cost–consequences analysis (CCA) comparing topotecan with paclitaxel, etoposide and altretamine and one cost-effectiveness analysis (CEA) comparing topotecan with paclitaxel.

Quality of clinical effectiveness data

Both clinical effectiveness studies (trial 30-49 and 039) were of reasonable quality, although it was unclear whether either performed valid intention-to-treat analyses. In addition, trial 30-49 failed to state whether the outcome assessors were blinded to treatment allocation.

Quality of economic evaluations

The CCA (comparing topotecan with three comparators) was of poor quality and of little relevance to the UK NHS. The CMA and CEA were of reasonable quality overall and relevant to the UK NHS. However, both, in particular the CEA, suffered from methodological problems, and thus their findings should be interpreted with caution.

Assessment of clinical effectiveness

The assessment of clinical effectiveness was based on limited data. Only two trials with a total of 709 participants were identified. In general, with a few minor exceptions, there were no statistically significant differences between topotecan and paclitaxel, or topotecan and caelyx in survival, response rate, median time to response, median duration of response and quality of life. Significant differences that were reported were mainly identified in subgroup analyses (Pt-sensitive disease and disease without ascites) of questionable validity and their relevance to a general advanced ovarian cancer patient population undergoing second-line chemotherapy is unclear. However, statistically significant differences were observed in the incidence of adverse effects. Topotecan was associated with increased incidences of haematological toxicities (including neutropenia, leukopenia, anaemia and thrombocytopenia), alopecia, nausea and vomiting. Caelyx-treated patients suffered from significantly increased incidences of Palmar–Plantar erythrodysesthesia, stomatitis, mucous membrane disorders and skin rashes. Paclitaxel was associated with significant increases in alopecia, arthralgia, myalgia, neuropathy, paraesthesiae, skeletal pain and flushing.

Assessment of cost-effectiveness

The assessment of cost-effectiveness was also based on limited data, with three evaluations identified, one of which was not relevant. The two remaining studies, comparing topotecan with paclitaxel (CEA) and topotecan with caelyx (CMA), both used effectiveness data from multicentre RCTs and based their costs on 1999/2000 UK sources. The evaluations were conducted from a UK NHS perspective and findings presented in £/Euros. Topotecan for the second-line treatment of advanced ovarian cancer was shown to be more cost-effective than paclitaxel (£32,513 versus £46,186 per person in terms of any response (complete or partial), incremental cost-effectiveness = £3065) in all respects except cost per time without toxicity or symptoms, but less cost-effective than caelyx (£14,023 versus £9979 per person regardless of whether the patient responded). However, direct comparisons of the cost findings between the two studies is difficult because they used different designs, different time horizons for the cost analyses and the findings were presented as costs per person for only patients who responded in one study (topotecan versus paclitaxel) and costs per person regardless of whether they responded in the other study (topotecan versus caelyx).

Conclusions

This review indicates that there is little evidence in the form of RCTs on which to base an assessment of the effectiveness of topotecan as second-line therapy for advanced ovarian cancer. The evidence suggests there were no statistically significant differences overall between topotecan and paclitaxel, or topotecan and caelyx in clinical outcomes. However, statistically significant differences were observed in the incidence of adverse effects. The clinical significance of the findings is not discussed. Overall, the effects of topotecan could at best be described as modest, but the alternative agents offer no real advantages except fewer side-effects and possibly improved cost-effectiveness. Both of the clinical effectiveness studies on which this evidence is based had methodological flaws, the most serious being the lack of a blinded assessor in the topotecan versus caelyx trial, which is important for unbiased assessment of response outcomes. The economic evaluations also suffered from a number of potential problems.

Recommendations for research

Further good quality RCTs and CEAs are required comparing topotecan with other licensed and

potentially useful (soon to be licensed) second-line treatments for ovarian cancer. At present, it is difficult to make any decisions about topotecan and other drugs for second-line therapy without good quality direct comparisons. In view of the ongoing studies identified, an update of the current review should be considered in approximately 18 months (Summer 2002) or possibly sooner if the recently commissioned National Institute for Clinical Excellence review of caelyx for ovarian cancer identifies additional data relevant to topotecan.

Publication

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