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

Caroline Main[1], Gill Norman[1], Lisa Stirk[1], Dan Stark[2], Rob Riemsma[1]

[1] Centre for Reviews and Dissemination, University of York, UK. [2] Department of Oncology, Bradford Royal Infirmary, UK

Background

Ovarian cancer is the most common gynaecological cancer, and the fourth most common cause of cancer death in women. The prognosis is generally poor, due 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 NICE 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). The majority of patients ultimately relapse and require re-challenging with second-line therapy. Treatment with pegylated liposomal doxorubicin hydrochloride (PLDH), topotecan or paclitaxel may therefore be considered alongside other drugs licensed for second-line therapy in advanced ovarian cancer.

Objective

To assess the clinical effectiveness 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

- This review was an up-date of three earlier systematic reviews. Seventeen electronic databases were therefore searched from 2000-2004, as all previous searches had been conducted up to 2000. The review up-dated the previous reviews commissioned by NICE on the use of topotecan[1] and pegylated liposomal doxorubicin hydrochloride[2] for ovarian cancer, and taxanes for the treatment of advanced breast and ovarian cancer.[3]
- Randomised controlled trials (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.
- Two reviewers independently assessed titles and abstracts and full papers.
- One reviewer carried out data extraction and quality assessment and this was checked for accuracy by a second reviewer.
- The included trials were clinically and methodological heterogeneous, and could not be combined in a meta-analysis. A narrative synthesis of the trials was therefore undertaken.

Results

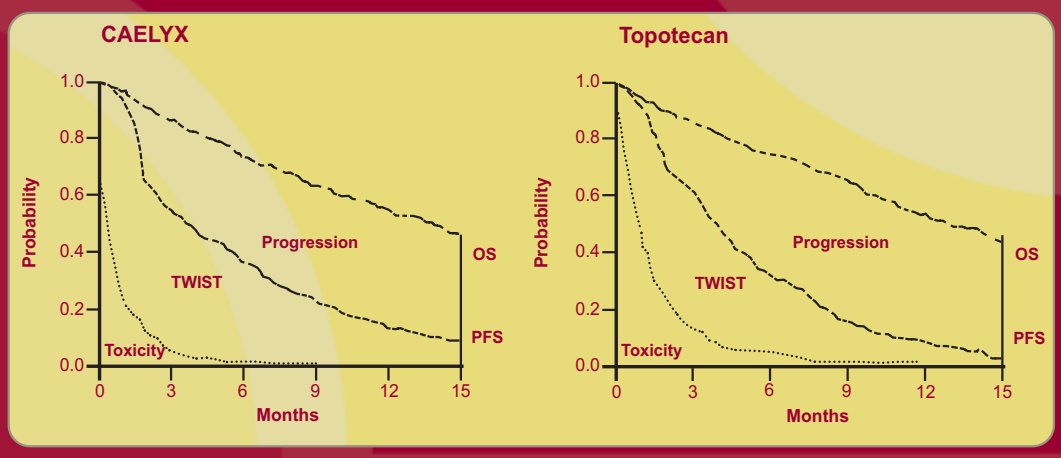
- Nine RCTs were included (see Table 1). In five trials, both the comparators were used within their licensed indication. Three of these trials included participants with both platinum-resistant and platinum-sensitive disease, whilst a further two trials only included participants with platinum-sensitive disease. Four trials were included in which one of the comparators was used outside its licensed indication. All of the trials were of reasonable quality.
- PLDH was marginally more effective than topotecan in terms of overall survival in the total trial population that included both participants with platinum-sensitive disease and platinum-resistant disease. This result appeared to be driven by the more significant benefit of PLDH treatment in the platinum-sensitive sub-group of patients. There were no significant differences between PLDH and topotecan in relation to progression-free survival, response or quality of life as assessed by both the European Organization for Research and Treatment of Cancer Quality of Life (EORTC) QLQ-C30 questionnaire and Q-TwiST survival analysis (see Figure 1).
- No significant differences between topotecan and paclitaxel, or PLDH and paclitaxel were observed for overall survival. The trial of PLDH versus paclitaxel was terminated prematurely, therefore this result should be interpreted with caution.
- 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.
- Paclitaxel in combination with platinum based chemotherapy was more effective than platinum monotherapy in relation to both overall survival and progression free survival. There were no significant treatment benefits observed for combination therapy for response rates or quality of life.
- All the chemotherapy regimens were associated with significant grade 3 and 4 toxicities. However toxicity profiles differed considerably between the comparators.

Table 1: Summary of the comparators included

Comparators included in the review	Paclitaxel	Topotecan (i.v)	PLDH	Paclitaxel combination	Platinum	CAP[1]	Oxaliplatin	Oral topotecan
Overall patient population								
Trial 30-49[4]		•	•					
Trial 039[5]	•	•						
Trial 30-57[6]	•		•					
Platinum sensitive patients								
Cantu et al.[7]	•					•		
ICON 4/AGO-OVAR 2.2[8]				•	•			
Unlicensed comparator								
Piccart et al.[9]	•						•	
Rosenberg et al.[10]	••							
Omura et al.[11]	••							
Gore et al.[12]		•						•

[1] Cyclophosphamide, doxorubicin and cisplatin

Figure 1: Q-TwiST survival analysis – partitioned survival curves for PLDH versus topotecan



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For further details contact Caroline Main cm35@york.ac.uk

Review Conclusions

Patients with platinum-resistant disease: there was a low probability of response to treatment with PLDH, topotecan or paclitaxel, and little difference between the comparators in relation to overall survival. The comparators did however differ significantly in their toxicity profiles. Given the low survival times and response rates the maintenance of quality of life, control of symptoms and toxicity are paramount. It can be suggested that this group of patients may benefit from being included in further trials of new drugs.

Patients with platinum-sensitive disease: a range of survival times were observed across the trials. The most favourable survival times and response rates were observed for paclitaxel and platinum combination therapy. Re-challenge with combination therapy may therefore be more beneficial than re-challenge with a single agent regimen. Some evidence from a sub-group analysis suggested that PLDH was more effective than topotecan in terms of treatment with a single agent compound. The toxicity profiles were again different across the trials. Patient and physician choice as to the potential toxicities associated with the comparators, and the patients' ability and willingness to tolerate these are important.

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