Topotecan plus carboplatin and paclitaxel in first-line treatment of advanced ovarian cancer: a meta-analysis of randomized controlled trials

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CRD summary
The review concluded that the addition of topotecan to carboplatin and paclitaxel did not improve survival outcomes (compared with carboplatin and paclitaxel), and caused more haematological toxicity in patients with advanced ovarian cancer. The limited evaluation of trial quality, coupled with the lack of reporting of toxicity event numbers, means the reliability of the authors' conclusion is unclear.

Authors' objectives
To evaluate whether the addition of topotecan could improve the efficacy of carboplatin and paclitaxel in the first-line treatment of advanced epithelial ovarian cancer.

Searching
MEDLINE and EMBASE were searched to May 2011; Cochrane Central Register of Controlled Trials (CENTRAL) was searched to April 2011; and the Specialised Register of the Cochrane Gynaecological Cancer Review Group was searched. There were no language restrictions. Search terms were reported. Investigators of ongoing trials were contacted to help identify unpublished studies. Reference lists of relevant studies, and the proceedings of the Annual Meetings of the American Society of Clinical Oncology were examined.

Study selection
Randomised controlled trials (RCTs) that compared topotecan plus carboplatin and paclitaxel versus carboplatin and paclitaxel in patients with advanced ovarian cancer were eligible for inclusion. Trials had to report one of the review primary outcomes (progression free survival or overall survival) or a secondary outcome (overall response rate or toxicity). Overall response rate was defined as complete response rate plus partial response rate. Toxicity included leucopenia, neutropenia, anaemia, thrombopenia, nausea, and vomiting.

Topotecan use was sequential in half the included trials and combined in the other half. Most trials used a topotecan dose of 1.25mg/m² (one used a dose of 1.5mg/m²). All trials used paclitaxel at a dose of 175mg/m²; carboplatin doses were reported as being 5 or 6 (area under the curve). Disease stages ranged from IC to IV. Mean participant ages ranged from 55 to 60 years. Trials were published from 2004 up to 2010.

The authors did not state how many reviewers selected studies.

Assessment of study quality
Trial quality was assessed using the Jadad scale using criteria of randomisation, blinding, and withdrawals/drop-outs. The maximum possible score was 5 points. Trials that scored 3 or more points were considered to be of high quality.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Intention-to-treat data (where possible) were extracted to calculate hazard ratios or relative risks with 95% confidence intervals.

Two reviewers independently extracted data with disagreements resolved by discussion, or by a third reviewer.

Methods of synthesis
Meta-analyses were performed to calculate pooled hazard ratios or risk ratios using a random-effects model. Heterogeneity was assessed using $I^2$.

Results of the review
Four RCTs (3,632 patients) were included in the review. All trials scored 3 points on the Jadad scale.

No significant differences between treatment groups were observed for progression-free survival (three RCTs), overall survival (two RCTs), or overall response rate (two RCTs).

There were significantly higher rates in the topotecan plus carboplatin and paclitaxel group for the toxicity outcomes of grade 3-4 leucopenia (RR 2.51, 95% CI 1.13 to 5.57; two RCTs), neutropenia (RR 1.44, 1.25 to 1.65; two RCTs), anaemia (RR 2.75, 95% CI 1.97 to 3.84; two RCTs), and thrombopenia (RR 5.00, 95% CI 3.50 to 7.15; two RCTs). No significant differences were observed for grade 3-4 nausea or for vomiting.

There was no evidence of statistical heterogeneity in any of the analyses.

Authors’ conclusions
Topotecan plus carboplatin and paclitaxel did not improve survival outcomes (compared with carboplatin and paclitaxel), and caused more haematological toxicity for advanced ovarian cancer.

CRD commentary
The review addressed a clear question and was supported by reproducible eligibility criteria (although no population criteria details, beyond those in the review title, were provided). Attempts to identify relevant studies in any language were undertaken by searching electronic databases and attempts were also made specifically to identify unpublished studies. Suitable methods were employed to reduce the risks of reviewer error and bias for the data extraction process, but details were not reported for the study selection and quality assessment processes.

Trial quality was assessed using the Jadad scale. This produced limited evaluations, since allocation concealment methods (an important potential source of bias) were not assessed, and only the reporting of withdrawals and drop-outs was assessed (rather than whether they may bias trial results). Sufficient population and treatment details were provided. Appropriate methods were used to pool data and assess heterogeneity. However, the absence of actual event numbers for the toxicity outcomes made it difficult to evaluate the real value of the pooled results. This was because the possibility of results obtained by chance could be ruled out.

The limited evaluation of trial quality, coupled with the lack of reporting of toxicity event numbers, means the reliability of the authors' conclusion is unclear.

Implications of the review for practice and research
Practice: The authors stated that carboplatin plus paclitaxel remains the standard of care for patients with advanced ovarian cancer.

Research: The authors did not state any implications for research.

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