Systematic review of first-line chemotherapy for newly diagnosed postoperative patients with stage II, III, or IV epithelial ovarian cancer

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Authors' objectives
To assess the most effective post-operative chemotherapy regimen for women with newly diagnosed stage II, III, or IV epithelial ovarian cancer.

Searching
MEDLINE, Cancerlit, CINAHL, HealthSTAR and the Cochrane Library were searched for full papers or abstracts published in English between 1980 and April 2001; the search terms were reported. The authors also searched the proceedings of the American Society of Clinical Oncology (1999 to 2001), the International Gynecologic Cancer Society (2000), the 10th European Conference on Clinical Oncology, and the reference lists of papers and review articles for additional studies.

Study selection
Study designs of evaluations included in the review
Meta-analyses and randomised controlled trials (RCTs) were eligible for inclusion. The authors did not provide details about the duration of the interventions or the minimum follow-up periods.

Specific interventions included in the review
Studies of any first-line post-operative chemotherapy for ovarian cancer were considered for inclusion. Of particular interest were studies comparing platinum-based chemotherapy with and without paclitaxel, and studies comparing paclitaxel plus carboplatin versus paclitaxel plus cisplatin. Studies that evaluated the use of chemotherapy with bone marrow or stem cell transplantation were excluded. The drugs included in the review, in varying combinations, were paclitaxel, cisplatin, cyclophosphamide, carboplatin, doxorubicin and docetaxel. The exact doses, duration, and timing of treatment varied considerably between the studies. Details of the interventions were tabulated in the review.

Participants included in the review
Studies of women with newly diagnosed stage II, III (micro or macro), or IV epithelial ovarian cancer were eligible for inclusion. The authors described the characteristics of the patients and disease for some of the primary studies, but did not provide overall summary statistics for all participants included in the review (e.g. age range, mean duration of disease).

Outcomes assessed in the review
Studies that reported data on survival for each intervention group were eligible for inclusion. In addition, the authors included data on adverse effects, quality of life and dose-response relationships. The outcomes were measured using definitions from the primary studies.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The authors extracted data on participant numbers, disease stage, intervention, median survival, adverse effects, and other outcomes reported in the primary studies.

Methods of synthesis
How were the studies combined?
The authors provided a narrative synthesis of findings and drew on pooled data from published meta-analyses. Where no published meta-analysis was available, they pooled data on grade 3 and 4 adverse effects using a random-effects model. The results were expressed as risk ratios with associated 95% confidence intervals (CIs).

How were differences between studies investigated?
The authors described differences between the studies, and conducted tests for statistical heterogeneity to ascertain the appropriateness of pooling the data quantitatively. They did not report the type of tests used to assess differences between the studies.

Results of the review
Two meta-analyses of individual patient data (see Other Publications of Related Interest nos.1-2) and 10 RCTs were included. The authors did not report the total number of participants included in the review. Data from more than 3,000 women were included in the meta-analyses, although it is difficult to cite an exact number due to the inclusion of multiple meta-analyses in one paper. A total of 5,815 women participated in seven of the RCTs included in the review (range: 208 to 2,074 per study); the number of participants in the other 3 trials was unclear.

Survival.
Platinum without paclitaxel (1 meta-analysis): a published meta-analysis of 9 RCTs (n=1,704) found that chemotherapy regimens containing platinum had a survival advantage over regimens not containing platinum (hazard ratio for death 0.88, 95% CI: 0.79, 0.98, P=0.02).

Platinum plus paclitaxel (5 randomised trials): it is unclear whether adding paclitaxel to platinum-based regimens improves survival. Five randomised trials have drawn varying conclusions, depending on the exact regimen used and the participants' disease stage.

Single- versus multi-agent platinum-based chemotherapy without paclitaxel (1 meta-analysis and 1 randomised trial): a published meta-analysis of data from 9 trials (n=1,095) found no significant difference in survival among women receiving single- versus multi-agent platinum-based chemotherapy (hazard ratio 0.91, 95% CI: 0.8, 1.05, P=0.21); similarly, no single randomised trial has found conclusively that multi-agent platinum-based chemotherapy improves survival over single-agent regimens.

Anthracyclines without paclitaxel (1 meta-analysis): the effect of adding anthracyclines to chemotherapy remains uncertain. A published meta-analysis of data from 4 trials (n=1,194) found that cyclophosphamide plus doxorubicin plus cisplatin improved survival compared with cisplatin plus cyclophosphamide (15% reduction in the odds of death, P=0.02). However, it was unclear to what extent the difference in survival was due to greater dose intensity or to the addition of doxorubicin.

Carboplatin versus cisplatin (1 meta-analysis and 2 randomised trials): the authors found no significant difference in survival between carboplatin versus cisplatin. One published meta-analysis of data from 12 trials (n=2,219) found no difference in survival between women receiving cisplatin or carboplatin as a single agent or as part of multi-agent therapy (cisplatin versus carboplatin, hazard ratio 1.02, 95% CI: 0.93, 1.12, P=0.66). None of the regimens in this meta-analysis included paclitaxel. Two additional randomised trials evaluated carboplatin plus paclitaxel versus cisplatin plus paclitaxel. Neither trial found a significant difference in survival between groups.

Adverse effects (14 randomised trials and 1 meta-analysis by the authors).
Ten trials found significant differences between carboplatin and cisplatin in acute toxicity. The authors pooled data on grade 3 and 4 adverse effects where possible. Haematological adverse effects were more frequent with carboplatin than with cisplatin (risk ratio for grade 3 to 4 thrombocytopenia 0.19, 95% CI: 0.14, 0.25). Non-haematological adverse effects were more frequent with cisplatin (risk ratio for grade 3 to 4 nausea and vomiting 1.63, 95% CI: 1.28, 2.07; risk ratio for neutropenia 2.40, 95% CI: 1.67, 3.45). The authors noted that the studies were heterogeneous, but did not report test statistics or P-values. The full article also described adverse effects from other regimens.
No published meta-analysis was available for paclitaxel-based first-line therapy. The authors planned to pool mortality data, but did not do so because of study heterogeneity.

**Authors’ conclusions**

Intravenous carboplatin plus paclitaxel is the optimal post-operative chemotherapy regimen for women with newly diagnosed stage II to IV epithelial ovarian cancer. Intravenous cisplatin plus paclitaxel could also be considered. Intravenous carboplatin alone may be considered where paclitaxel is contraindicated, or in women who wish to avoid the adverse effects of paclitaxel.

**CRD commentary**

This review addressed a defined research question. The general inclusion and exclusion criteria were provided and the search strategy was reasonable. It is likely that most studies meeting the inclusion criteria were identified by the search strategy; however, some important studies might have been excluded. The authors excluded unpublished studies (apart from those presented at conferences) and studies reported in languages other than English. They did not consider whether publication bias or language bias may have impacted on the findings of the review.

It was difficult to assess the overall quality of the review because the authors did not describe their methods in any detail. They did not report the methods used to assess the relevance and validity of studies included in the review, nor did they describe how the data were extracted or what quality checks were in place. They also omitted some details about the primary studies, such as patient gender, follow-up duration and follow-up rate. The lack of detail for participant characteristics makes it more difficult to generalise the findings to specific patient sub-populations.

The authors relied on two published meta-analyses to pool some of the data, but did not describe any procedures to check the validity, assumptions and methods of these meta-analyses. Given the varying treatment regimens in each study, it may not have been appropriate to combine the data in this way. The authors did not pool data on paclitaxel-based regimens, although the decision not to pool the data quantitatively seems appropriate given the differences between the studies. However, the authors did pool data on grade 3 and 4 adverse effects in other regimens, even though they noted that the studies were heterogeneous. They did not report test statistics or P-values. This pooled data should be interpreted cautiously given the differences between the studies.

The authors outlined implications for clinical practice and presented their recommendations clearly. The conclusions appear to be supported by the data presented. The authors were unable to recommend optimal doses, owing to a lack of evidence, thus leaving one component of their research question unanswered.

**Implications of the review for practice and research**

Practice: The authors suggested that carboplatin plus paclitaxel should be the standard treatment for stage II to IV ovarian cancer. Carboplatin may be administered in doses ranging from 4 to 6 AUC. Paclitaxel may be administered in doses ranging from 135 to 175 mg/m2 over a 3-hour period. Single-agent carboplatin may be used in women who wish to minimise toxicity, especially those who are elderly or medically infirm.

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

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