Survival benefits with diverse chemotherapy regimens for ovarian cancer: meta-analysis of multiple treatments

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CRD summary
The authors concluded that platinum and taxane-based combination therapy with intraperitoneal administration can improve survival in comparison with regimens containing neither. Taxanes without platinum do not appear to provide any clear survival benefit. Poor reporting of review methods and the lack of an assessment of validity mean that the reliability of the authors’ conclusions is unclear.

Authors' objectives
To conduct an overview of all randomised trials comparing chemotherapy regimens in patients with ovarian cancer.

Searching
MEDLINE, EMBASE and the Cochrane CENTRAL Register were searched from 1965 to January 2006; the search terms were reported. Reference lists of retrieved trials and previous meta-analyses were checked. Cross-searches were performed on MEDLINE using authors from eligible trials. Journals with the highest number of electronically identified trials were also handsearched. Only trials published in English, German, French or Italian were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials were eligible for inclusion. Non-randomised trials and pseudo-randomised trials with alternate allocation were excluded.

Specific interventions included in the review
Trials that compared at least two arms of different chemotherapy regimens (different agents and/or schedules) regardless of line of treatment were eligible for inclusion. Trials with at least three arms were eligible for inclusion provided at least two arms addressed an eligible comparison; the non-eligible arm was excluded. Comparisons of chemotherapy against no chemotherapy (such as best supportive care) were excluded.

The type of chemotherapy regimen was categorised according to whether it involved platinum, taxane, both or neither; whether a combination of agents or monotherapy were used; and whether intraperitoneal administration of any agents was used or not. The majority of trials reported no previous chemotherapy having been administered. A total of 120 different regimens were tested across the included trials. Only 6 monotherapies and 15 combinations of different agents were tested in at least four trial arms each. Doses and schedules of the same regimen differed across trials. The most commonly used regimen was cisplatin, cyclophosphamide and doxorubicin (34 arms); followed by cisplatin and cyclophosphamide (33 arms), paclitaxel (24 arms), cisplatin (23 arms), carboplatin (21 arms), and carboplatin and paclitaxel (19 arms).

Participants included in the review
Trials in at least 5 patients with ovarian cancer at any stage of the disease were eligible for inclusion. Data on other malignancies or nonepithelial ovarian cancer were excluded. Where reported in the included studies, the percentage of patients with poor performance status ranged from 0 to 52%. Only 2 trials reported the majority of patients having stage 1 disease.

Outcomes assessed in the review
Studies that assessed median survival times and the numbers of deaths per treatment arm were included.

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
Two investigators independently extracted the data. Any disagreements were resolved by consensus. For trials comparing at least two different types of chemotherapy regimens, the hazard ratio (HR) and its variance and 95% confidence interval (CI) were extracted or estimated.

Methods of synthesis
How were the studies combined?
The studies were combined using a multiple treatment meta-analysis using a linear mixed-effects model. The log HRs for each comparison of two different types of treatment were summarised using a random-effects model. One multiple treatment meta-analysis addressed all eligible trials and compared different types of chemotherapy. The probability of each type of treatment being the best at prolonging survival was estimated using Monte Carlo simulations.

How were differences between studies investigated?
Heterogeneity between the studies was assessed using the I-squared statistic. Exchangeability of studies was assessed by examining heterogeneity and incoherence (disagreement between direct and indirect estimates of relative effectiveness of two treatments). Two separate analyses were also conducted: one included only trials that addressed first-line treatment and the other included trials that addressed second-line treatment.

Results of the review
A total of 198 randomised controlled trials (n=38,440 women) were included. Eighty-two of these (n=15,609) compared different types of regimens and were included in the multiple treatment meta-analysis.

Comparison of chemotherapy regimens.
Six (n=1,154) of the 116 trials that compared only regimens of the same type found statistically significant differences in survival, with median survival ranging from 13.1 to more than 35 months. However, this result did not go beyond what might be expected by chance. In addition, trials following different regimens found only small differences and the probability that these findings were due to chance could not be ruled out.

Comparisons of different types of regimens.
Sixty of the 82 trials that compared different types of regimens contained survival data and were included in the synthesis (16,478 randomly assigned participants; 15,609 in survival analyses). Heterogeneity was found for the comparison of platinum-based combinations versus platinum and taxane-based combinations (I-squared 70%; 4 trials).

Direct comparisons found that platinum monotherapy was statistically significantly more effective than monotherapy with a nonplatinum, nontaxane agent (HR 0.63, 95% CI: 0.48, 0.83), while a platinum-based combination was more effective than monotherapy (HR 0.78, 95% CI: 0.64, 0.94) or combinations involving neither platinum nor taxanes (HR 0.77, 95% CI: 0.69, 0.87). Combinations involving neither platinum nor taxane were better than monotherapy with such agents (HR 1.20, 95% CI: 1.06, 1.36). Platinum and taxane-based combinations were more effective than platinum-based combinations (HR 1.28, 95% CI: 1.07, 1.53), and intraperitoneal administration improved survival with platinum and taxane-based combinations (HR 1.28, 95% CI: 1.07, 1.53).

Multiple treatment meta-analyses.
Sixty trials (15,609 women) reported survival data and were included in the multiple treatment analyses.

Based on multiple-treatment analyses, the following treatment regimens were significantly more effective than monotherapy with non intraperitoneal, nonplatinum, nontaxane regimens: non intraperitoneal platinum-based monotherapy (HR 0.68, 95% CI: 0.59, 0.78), the combination of nonplatinum and nontaxane agents (HR 0.87, 95% CI: 0.78, 0.97), platinum-based combination treatment (HR 0.70, 95% CI: 0.62, 0.80), intraperitoneal platinum-based combination treatment (HR 0.60, 95% CI: 0.46, 0.79), platinum plus taxane-based combination (HR 0.58, 95% CI:...
0.49, 0.69), and intraperitoneal platinum plus taxane-based combination treatment (HR 0.45, 95% CI: 0.33, 0.6).

Using Monte Carlo simulations it was 92% likely that combinations of platinum and taxane with intraperitoneal administration were the most effective regimens, and 98% likely that the most effective regimen included intraperitoneal administration.

No important incoherence between comparisons was detected (incoherence was 0.001).

Second-line results appeared to show improved survival with platinum-taxane combinations. However, owing to the small number of trials assessing second-line treatment, the multiple treatment meta-analysis was considered potentially unreliable.

**Authors’ conclusions**
A platinum and taxane-based combination therapy with intraperitoneal administration can improve survival compared with regimens containing neither. More than half of this benefit may be achieved with standard platinum-based combination regimens. Taxanes without platinum do not appear to provide any clear survival benefit.

**CRD commentary**
Inclusion criteria were clearly defined for the interventions, outcomes and study designs, and broadly defined for the participants. A range of relevant sources were searched, but no efforts were made to locate unpublished material and only publications in English, French, German or Italian were included; it is therefore possible that some relevant studies could have been missed. Publication bias was not assessed. The methods used to select the studies were not reported, so it is difficult to comment on the risk of bias and errors being introduced during the review process. Efforts were made to reduce reviewer error and bias at the data extraction stage. Validity was not assessed, thus the results from these studies and any synthesis might not be reliable. Statistical heterogeneity was assessed and the studies were pooled using meta-analysis, which seemed appropriate. Incomplete reporting of review methods and the lack of an assessment of validity mean that the reliability of the authors’ conclusions is unclear.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated the need for future trials designed to fill in gaps where evidence is minimal or there is no information. Infrastructure support would be needed for an efficient strategic plan for clinical research. In addition, clinical trials cooperative groups need to develop complementary trials to reduce duplication and perform joint trials where appropriate.

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