Combination of docetaxel-carboplatin for adjuvant chemotherapy of epithelial ovarian, primary peritoneal and fallopian tube cancers: a meta-analysis

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CRD summary
Treatment with combined docetaxel-carboplatin for advanced epithelial ovarian, primary peritoneal or fallopian tube cancers had significantly higher haematological toxicology than that for combinations of paclitaxel-carboplatin or docetaxel-cisplatin. Clinical responses of the three drug combinations were similar. The reliability of the authors’ conclusions is unclear due to limited evidence, presence of heterogeneity and uncertainties about the quality of included studies.

Authors’ objectives
To compare the safety and efficacy of combination docetaxel-carboplatin with combination non docetaxel-carboplatin as first-line chemotherapy for advanced epithelial ovarian, primary peritoneal or fallopian tube cancers.

Searching
MEDLINE (from 1993), EMBASE (from 1980), Medion, Science Citation Index Expanded and The Cochrane Library were searched to 2010 for publications in English and other languages; search terms were reported. Bibliographies of each retrieved article, relevant reviews and conference abstracts were handsearched. Experts in the field were contacted.

Study selection
Randomised controlled trials (RCTs) and case-control studies that compared combination docetaxel-carboplatin therapy with another first-line combination therapy not based on docetaxel-carboplatin were eligible for inclusion. Studies of patients with a histologically confirmed International Federation of Gynaecology and Obstetrics (FIGO) stage diagnosis of advanced epithelial ovarian, primary peritoneal or fallopian tube cancers were eligible for inclusion.

Eligible outcomes included overall, partial and complete response, stable and progressive disease and toxicity (haematological, gastrointestinal and neurotoxicity were included). Survival rate and allergic reaction were also reported.

The included studies compared docetaxel-carboplatin with paclitaxel-carboplatin in most trials or docetaxel-cisplatin (one RCT). Dose ranges were AUC 5 or 6 for carboplatin, 60 to 75mg/m² docetaxel, 135 to 175mg/m² paclitaxel and 60mg/m² cisplatin given every 21 days for three to six cycles. In one study the number of cycles given was related to cancer stage. All patients in the RCTs and most patients in the case-control studies had ovarian cancer; other patients had peritoneal or fallopian tube cancers. Median age ranged from 51.5 years to 63 years. Haematological toxicity reported included neutropenia, thrombocytopenia and anaemia. Gastrointestinal toxicity reported included nausea and vomiting. All studies except one reported the grade of neutropenia. One study reported grades of thrombocytopenia and anaemia (grades 1 to 4).

The authors did not report how many reviewers performed study selection.

Assessment of study quality
No formal validity assessment was reported. Some relevant data were reported and included study type, intention-to-treat analysis (ITT) and blinding. A rudimentary quality grade was assigned to the studies: A for RCTs and D for case-control studies.

The author reported neither how many reviewers performed the validity assessment nor whether it was performed in a structured manner.
Data extraction
Two independent reviewers extracted the number of events for each outcome in order to calculate odds ratios (OR) with 95% confidence intervals (CI).

Methods of synthesis
Odds ratios were pooled using a random-effects model (DerSimonian and Laird). Between-study heterogeneity was determined using Cochran's Q and $I^2$. No meta-analysis was performed for survival rate and progress-free survival since data were available for only two studies and one was much smaller than the other. Publication bias was assessed visually using funnel plots. Sensitivity analyses were performed to find the effect of study type. Subgroup analyses were performed by type of toxicity and type of response.

Results of the review
Five studies were identified (n=1,430): three RCTs (n=1,148, range 29 to 1,069) and two case-control studies (n=40 and n=242). All the RCTs used ITT analysis. None of the studies were double-blind placebo-controlled studies.

There was a significantly higher level of grade 3 or 4 haematological toxicity with docetaxel-carboplatin versus non-docetaxel-carboplatin treatment (OR 4.41, 95% CI 3.06 to 6.36, $I^2=76.3%$; four studies, significant heterogeneity).

There was no significant difference between docetaxel-carboplatin and non-docetaxel-carboplatin treatment for neurotoxicity ($I^2=76.4%$; four studies, significant heterogeneity), gastrointestinal toxicity ($I^2=20.9%$; three studies) and allergic reaction ($I^2=0%$; three studies).

The total number of events for all four toxicities was significantly lower for non-docetaxel-carboplatin treatment than for docetaxel-carboplatin treatment (OR 1.33, 95% CI 1.13 to 1.56, $I^2=83.6%$, significant heterogeneity).

There was no significant difference between docetaxel-carboplatin and non-docetaxel-carboplatin treatment for complete response ($I^2=0%$; three studies), partial response ($I^2=0%$; three studies), stable disease ($I^2=0%$; three studies), progressive disease ($I^2=0%$; three studies) and total number of events for all four combined (clinical response) (OR 1.0, 95% CI 0.87 to 1.16, $I^2=0%$; three studies). All three analyses showed no significant heterogeneity.

No meta-analysis was performed for survival rate at two years or progress-free survival; data were available for two RCTs and neither gave significant results.

A funnel plot showed no evidence of publication bias.

Authors' conclusions
Safety of a combination of docetaxel-carboplatin was lower than that of combinations of paclitaxel-carboplatin or docetaxel-cisplatin. However, clinical responses of a combination of docetaxel-carboplatin were similar to those of combinations of paclitaxel-carboplatin or docetaxel-cisplatin.

CRD commentary
The review addressed a well-defined question in terms of participants, interventions and study design. Relevant outcomes were not precisely defined. Relevant databases were searched. There were no language restrictions. Efforts were made to identify unpublished studies and assess publication bias. Study quality was assessed, but only a rudimentary grade was assigned to the two study design types and little relevant information was reported. Two independent reviewers performed the data extraction; the authors did not report that other efforts were made to reduce error and bias in the review process. Relevant study details were reported, but no precise definition was reported for many outcomes.

Statistical heterogeneity was assessed and there was evidence for heterogeneity with some toxicological outcomes. The authors noted that there was heterogeneity in toxicology categories, dosages and the number of cycles in treatment regimes. The statistical method used for the meta-analysis of the RCTs seemed appropriate but, although the authors reported that a random-effects analysis was performed, the tables and discussion reported the results of a fixed-effect analysis. The authors reported that sensitivity analyses were performed but did not report the results clearly.
The reliability of the authors’ conclusions is unclear in view of the limited evidence presented, presence of heterogeneity for some outcomes and uncertainties about the quality of included studies.

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

**Practice:** The authors stated that paclitaxel-carboplatin and docetaxel-cisplatin were much safer than docetaxel-carboplatin in treating the common gynaecological malignant cancers, in particular for grades 3 and 4 neutropenia.

**Research:** The authors identified a need for further RCTs to compare survival rates for docetaxel-carboplatin and paclitaxel-carboplatin.

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