Meta-analysis comparing cisplatin total dose intensity and survival

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Authors' objectives
To determine whether increasing dose intensity for cisplatin/carboplatin alone, or in combination with other drugs, for first-line therapy improves median survival in stage III-IV ovarian cancer patients. The authors' realised objective was to identify important factors that determine outcome in terms of median survival.

Searching
MEDLINE and Cancerline were searched from 1976-1993 for English language studies. Keywords used were 'cisplatin', 'carboplatin' and 'ovarian neoplasm'. Reference lists from all retrieved articles were searched.

Study selection
Study designs of evaluations included in the review
Published prospective clinical trials. Twenty-one randomised controlled trials(RCTs) and 17 cohort studies were included. Planned doses, schedule and number of course for first-time therapy needed to be stated, and study must have included median survival data or an actuarial study curve.

Specific interventions included in the review
Cisplatin or carboplatin. Included study arms must have had patients treated with cisplatin or carboplatin. Drugs used in combination with cisplatin and carboplatin (i.e. cyclophosphamide, adriamycin and hexamethylmelamine) were used to calculate the global dose intensity.

Participants included in the review
Patients with stage III or IV ovarian cancer, including both optimally and suboptimally debulked patients. The patients must not have had any prior chemotherapy or radiotherapy.

Outcomes assessed in the review
Median survival was assessed.

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

Assessment of study quality
The studies were not evaluated for quality.

Data extraction
Two authors independently extracted the data and agreement was reached for each study.

Methods of synthesis
How were the studies combined?
The results were presented as the percentage of studies reporting the outcome of interest. Study arms were used as the unit of analysis rather than patients. Linear regression models were fitted with median survival as the dependent variable. The independent variables of the models included dose intensity, total dose intensity, global dose intensity and percentage of optimally debulked patients. Regression analyses were weighted by the sample size.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

**Results of the review**
Thirty-eight studies with 61 treatment arms, with a total of 4,118 patients, were included.

No significant correlation was found between dose intensity and median survival (p=0.90) or total dose intensity of cisplatin and median survival (p=0.11). Of ten variables tested, percentage of patients optimally debulked, proportion of mucinous tumour and total amount and dose intensity of all drugs combined were found to have a significant correlation to median survival. All studies with a global dose intensity of less than 20 and <20% patients optimally debulked had a median survival of less than 20 months. 77% of studies with a global dose intensity of more than 20 and >20% patients optimally debulked had a median survival of more than 20 months. Single-agent chemotherapy had the worst outcome and there was little differences between two or more drugs for percentage of studies with >20 months' median survival (56.5% versus 63.3% respectively).

**Authors' conclusions**
Total dose intensity of all drugs and percentage optimally debulked are important factors that determine outcome in terms of survival. However, the aim of the review was to compare dose intensity against median survival and not debulking surgery against median survival. It is therefore likely that important studies examining debulking surgery were excluded from this analysis, which may alter the correlations found. Drawing the conclusion from this review that debulking surgery improves survival may be erroneous.

**CRD commentary**
It would be difficult for a non-specialist to make sense of this review. The authors use a range of acronyms throughout the review, and the data summarised is equivalent to data from observational studies, though randomised studies were included. The authors reported that there were no trials specifically addressing the objectives of the review. Thus, the meta-analysis reviewed published studies which asked a different question.

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