Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: a meta-analysis

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CRD summary
The authors concluded that neoadjuvant chemotherapy in place of primary surgical cytoreduction is associated with reduced survival time in patients with advanced ovarian cancer compared with initial surgery. Limitations in the review scope, search, reporting of review methods and analysis mean that these conclusions might not be reliable.

Authors' objectives
To assess the effects on survival of platinum-based neoadjuvant chemotherapy in lieu of primary cytoreductive surgery in patients with advanced ovarian cancer, and to evaluate the influence of other prognostic factors.

Searching
MEDLINE was searched from 1989 to September 2005 for studies published in the English language; the search terms were reported. In addition, reference lists of included studies were screened.

Study selection
Study designs of evaluations included in the review
Inclusion criteria were not specified for the study design. The review included individual cohorts of patients from studies of various designs including non-randomised Phase I pilot studies, non-randomised Phase II trials, retrospective case-control studies and retrospective studies.

Specific interventions included in the review
Studies that evaluated neoadjuvant chemotherapy that included cisplatin or carboplatin before attempted cytoreductive surgery were eligible for inclusion. The review defined neoadjuvant chemotherapy as a regimen aimed at avoiding a non-useful surgical procedure in patients considered optimally unresectable; studies had to report the mean number of pre-operative chemotherapy cycles and the proportion of patients who received taxanes as part of the chemotherapy regimen. Surgical cytoreduction had to be attempted after several cycles of systemic treatment and studies had to report the definition of maximal cytoreduction surgery (size of residual disease); the review defined maximal interval cytoreduction as residual disease with a maximum diameter of 2cm or less.

The included studies used fifteen different chemotherapeutic agents in various combinations (the drugs were listed) in addition to single-agent cisplatin or carboplatin. The median or mean number of pre-operative chemotherapy cycles before surgery ranged from 2.8 to 6 (based on 22 cohorts). The weighted mean maximal interval reduction was 65% (range: 0 to 100). The weighted mean proportion of patients receiving taxanes in each cohort was 47.7% (range: 0 to 100).

Participants included in the review
Studies in which more than 90% of the patients had stage III or IV epithelial ovarian cancer (according to International Federation of Gynecology and Obstetrics criteria) were eligible for inclusion. Patients undergoing neoadjuvant chemotherapy had to be diagnosed histologically using material obtained by biopsy. Studies had to report the proportion of patients with stage IV disease; this ranged from 0 to 76.5% and the weighted mean was 27.4% per cohort. The median age ranged from 53.6 to 68 years and the weighted median age of all cohorts was 61.1 years.

Outcomes assessed in the review
Studies that reported median survival time of individual cohorts of patients were eligible for inclusion in the review.

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.

Methods of synthesis
How were the studies combined?
Median or mean weighted values for potential prognostic variables of interest were presented together with the range of values across studies.

How were differences between studies investigated?
Simple linear regression models were used to evaluate the effect of the following variables on median survival time:
- median age of patients in the cohort; publication year; percentage of patients with stage IV disease; percentage of patients undergoing maximal interval cytoreductive surgery; mean or median number of pre-operative cycles of chemotherapy; and percentage of patients who received a taxane plus platinum chemotherapy. Regression models were weighted by the number of patients in each cohort. The linearity of variables included in models was examined and no nonlinear effects were found. The authors stated that there were too few observations in the final models to use multivariate models.

Results of the review
Twenty-one studies (providing 22 cohorts) were included (n=835).

Weighted median survival time was 24.5 months (range: 10.2 to 42; 22 cohorts).

There was a statistically significant association between median survival time and the following:
- the percentage of patients undergoing maximal reductive surgery (increased survival with increasing percentage undergoing maximal reductive surgery);
- the mean or median number of chemotherapy cycles (decreased survival with increased number of cycles);
- the percentage of patients receiving taxanes (increased survival with increased percentage receiving taxanes);
- the percentage of patients with stage IV disease (decreased survival with increased percentage of patients with stage IV disease); and
- year of publication (increased survival with more recent publication years).

There was no significant association between median/mean survival and median age of the cohort or residual tumour criteria.

Authors' conclusions
Compared with primary cytoreduction, neoadjuvant chemotherapy is associated with reduced survival time in patients with advanced ovarian cancer. Findings indicate that definitive surgery should be performed early in the course of treatment.

CRD commentary
The review stated a clear research question and inclusion criteria for the participants, intervention and outcomes were
defined. Limiting the search strategy to English language publications listed in one electronic database and reference lists of identified studies might have resulted in the omission of other relevant studies and increased the potential for publication and language bias. The methods used to select the studies and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer error and bias.

Simple linear regression appeared an appropriate method of exploring potential predictors of median survival. However, this method could not provide definitive answers to the review question. One limitation that the authors acknowledged was the lack of sufficient data for a multivariate analysis through which relationships between the various potential predictors of survival could be examined. In the conclusion the effect of neoadjuvant chemotherapy was compared with the effect of primary cytoreduction, but data were not provided in the review. In addition, the limited search and lack of reporting of review methods mean it is not possible to assess the reliability of these conclusions.

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

**Practice:** The authors stated that findings suggest that definitive surgery should be performed early in the course of treatment.

**Research:** The authors stated that additional studies on neoadjuvant chemotherapy are required to enable consistent identification of patients with surgically unresectable disease, and to determine the acceptable percentage of patients with advanced ovarian cancer that ought to be treated with neoadjuvant chemotherapy in lieu of initial surgery.

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