The role of intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a clinical practice guideline

Elit L, Oliver T, Coven A, Kwon J, Fung M K, Hirte H, Oza A, Gynecology Cancer Disease Site Group

CRD summary
This review found that, compared with intravenous chemotherapy, intraperitoneal chemotherapy improves survival for women with stage III ovarian cancer. However, increased toxicity and complication rates related to catheterisation need to be considered. Overall, the authors' conclusions appear reliable but should be interpreted with caution given the possibility of errors in the review process and the potential for language and publication bias.

Authors' objectives
To investigate intraperitoneal (IP) chemotherapy in women with stage III epithelial ovarian cancer.

Searching
MEDLINE (1966 to January 2006), EMBASE (1988 to January 2006), the Cochrane Library (Issue 4, 2005), PDQ, CMA Infobase and the National Guideline Clearinghouse were searched; the search terms were provided. Abstracts of conference proceedings of the American Society of Clinical Oncology (1997 to 2005) and the European Society for Medical Oncology (2002 to 2004) were also searched. Bibliographies of related literature and review articles were screened. Only articles published in English were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of first-line treatment involving IP-containing chemotherapy compared with first-line treatment involving intravenous (IV) chemotherapy alone were eligible for inclusion. Interventions that included immunotherapy, IP radioactive phosphorus or hyperthermia were excluded. Most studies compared combinations of cisplatin, paclitaxel, cyclophosphamide, epidoxorubicin or carboplatin by IV injection with combinations of caclitaxel, cisplatin, carboplatin, cyclophosphamide, epidoxorubicin or etoposide by IP injection. Most studies scheduled six cycles of treatment administered every 21 to 28 days. The proportion of patients receiving all treatment cycles of therapy ranged from 25 to 96%.

Participants included in the review
Studies of patients with advanced (stage III) epithelial ovarian cancer were eligible for inclusion. In the included studies, the median patient age ranged from 52.8 to 61 years. The patients had newly diagnosed epithelial ovarian cancer (ranging from stage II to stage IV). All trials specified that patients had to have adequate performance status, blood counts, and renal and hepatic function; in some studies patients were excluded if they had received any prior chemotherapy or radiotherapy. The majority of the patients were diagnosed with the histologic subtype serous adenocarcinoma. Where ethnicity was reported, the patients were predominantly white.

Outcomes assessed in the review
Studies assessing response to treatment, survival, toxicity, catheter-related complications and/or quality of life were eligible for inclusion. The outcomes assessed in the included studies were pathologic response rate, progression-free survival and/or overall survival, and quality of life.

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, but details of trial quality were reported in the ‘Results’ section.
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?
Survival data, estimated as relative risks (RRs), were pooled using a random-effects model.

How were differences between studies investigated?
Heterogeneity was assessed statistically using chi-squared and I-squared tests, and visually using forest plots.

Results of the review
Seven RCTs (n=1,806) were included in the review.

All 7 trials were non-blinded. Information on the randomisation procedure was provided in 4 trials. Power calculations were provided in 5 trials. All 7 trials reported that baseline characteristics were similar across treatment groups. Follow-up was more than 80% in 6 trials; the other trial only included evaluable patients (71% of included patients).

Response rates after second-look surgery (7 RCTs).
There were no statistically significant differences in clinical or pathologically confirmed complete response rates between any treatment arms for any trials. Complete pathologic response rates ranged from 36 to 58% for IV chemotherapy and from 36 to 57% for IP chemotherapy.

Progression-free survival (4 RCTs).
There were statistically significant 6-month improvements in median progression-free survival for patients who received IP chemotherapy compared with IV chemotherapy in 2 of the 3 phase III trials. Three trials (n=496) reported sufficient data to pool results and reported a pooled RR of 0.91 (95% confidence interval, CI: 0.85, 0.98) indicating that IP chemotherapy extends progression-free survival to a greater extent than IV chemotherapy.

Overall survival (6 RCTs).
Three phase III trials reported statistically significant improvements in median survival with IP chemotherapy compared with IV chemotherapy. The pooled analysis of 5-year overall survival showed a pooled RR of 0.88 (95% CI: 0.81, 0.95, p=0.002), indicating that IP chemotherapy leads to an approximately 12% improvement in survival compared with IV chemotherapy.

There was no evidence of statistical heterogeneity for pooled data for either progression-free survival or overall survival.

Adverse events associated with chemotherapy.
A greater proportion of grade 3 or 4 adverse events were detected in patients receiving IP chemotherapy compared with those receiving IV chemotherapy (p<=0.05). Adverse events reported were leucopenia (all studies), neutropenia (1 study), thrombocytopenia (1 study), gastrointestinal (2 studies), fatigue (1 study), renal or genitourinary (1 study), neurotoxicity (2 studies), metabolic (2 studies) and pain (1 study). The numbers of treatment-related deaths were similar across treatment groups. A relatively large proportion of patients discontinued IP treatment because of catheter-related complications (10 to 34%, where reported).

A greater proportion of patients undergoing IV chemotherapy completed all cycles of treatment (range: 32 to 95%) compared with patients undergoing IP chemotherapy (range: 25 to 76%).

Authors' conclusions
Cisplatin-containing IP chemotherapy may provide significant improvements in overall survival for patients with stage III ovarian cancer who are at high risk of disease recurrence. However, increased toxicity and complication rates related to catheterisation need to be considered.

**CRD commentary**

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. The search was reasonable and the search terms were reported. Only published English articles were included, which means that the review may be subject to language and publication bias. The methods used to select the studies, extract the data and assess study quality were not described, so it is not known whether any efforts were made to reduce reviewer error and bias. Although no formal validity assessment was reported, relevant aspects of study quality were discussed.

There was adequate information about the included studies. Statistical heterogeneity was assessed and combining the trials in a meta-analysis appears appropriate. Overall, the authors’ conclusions appear reliable but should be interpreted with some degree of caution given the possibility of bias and errors in the review process and the possibility of language and publication bias.

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

**Practice:** The authors stated that cisplatin-containing chemotherapy leads to improvements in overall survival and should be offered to patients.

**Research:** The authors stated that further RCTs should focus on optimal patient population and treatment regimen, including appropriate agents, infusate volume, schedule and dosage. The effectiveness of IP chemotherapy in other patient populations with ovarian cancer, including those with early-stage high-risk disease, should also be evaluated.

**Funding**

Cancer Care Ontario; Ontario Ministry of Health and Long-term Care.

**Bibliographic details**


This paper is produced by Cancer Care Ontario Practice Guidelines Initiative. It is available on the Internet and regularly updated. To ensure that you are viewing the most up to date version, go to the Cancer Care Ontario website at: https://www.cancercare.on.ca/toolbox/qualityguidelines/

**Original Paper URL**


**Other publications of related interest**


**Indexing Status**

Subject indexing assigned by CRD
MeSH
Antineoplastic Agents /administration & dosage /adverse effects; Infusions, Parenteral /adverse effects /methods; Neoplasms, Glandular and Epithelial /drug therapy; Ovarian Neoplasms /drug therapy; Practice Guidelines as Topic

AccessionNumber
12008008141

Date abstract record published
09/08/2008

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.