Intraperitoneal chemotherapy for patients with advanced ovarian cancer: a review of the evidence and standards for the delivery of care

CRD summary
The authors concluded that cisplatin-based intraperitoneal chemotherapy is associated with a significant survival benefit for women with optimally-debulked stage III epithelial ovarian cancer, compared with intravenous chemotherapy alone, but with an increase in short-term toxicity. These conclusions appear to be supported by the data presented, but poor reporting of the review methods makes it difficult to assess their reliability.

Authors' objectives
To evaluate the use of intraperitoneal (IP) chemotherapy as part of primary therapy for women with advanced ovarian cancer.

Searching
MEDLINE, EMBASE and the Cochrane Library were searched to December 2006. The reference lists of relevant articles and reviews were screened for additional citations.

Study selection
Randomised controlled trials (RCTs) of patients with stage III epithelial ovarian cancer were eligible for inclusion. The patients in eligible studies had stage II to stage IV disease and had undergone primary surgery to debulk tumours to two centimetres or less. Eligible studies compared primary treatment with IP chemotherapy (usually in combination with intravenous (IV) therapy) with primary treatment using IV therapy alone. The IP therapy used was in most cases cisplatin-based (50 to 200 mg/m²); other drugs used in one or both study arms were bleomycin, doxorubicin, fluorouracil, etoposide, carboplatin and paclitaxel (all either IP or IV), vinorelbine, ifosfamide and epidoxorubicin (all IV only). In many cases the intervention and control arms received differing total doses of chemotherapy or differing combinations of drugs, though the duration of therapy was the same in all cases (usually 6 cycles of 3 weeks). Chemotherapy completion rates varied widely among the studies. From 25 to 76% of women in the IP arms and 32 to 86% in the IV arms completed all cycles. In most studies completion rates were lower in the IP arm. Outcomes were not specified in the inclusion criteria. The outcomes reported in the review were survival, toxicity and quality of life.

The authors stated that a multidisciplinary panel conducted the searches, but no other details of the selection process were reported.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
For time-to-event outcomes, the authors calculated survival times and associated p-values for differences between the groups, and risk ratios (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs). For binary outcomes, percentages were calculated.

The authors stated that the evidence was reviewed at a consensus meeting, but no details of the data extraction process were reported.

Methods of synthesis
The data were combined in a narrative, grouped by outcome. In addition, data on complications were tabulated and survival date were pooled in meta-analysis to obtain a combined RR. Clinical and statistical heterogeneity were evaluated and discussed in the text.
Results of the review

Eight RCTs (n=1,826) were included.

The authors noted possible bias related to the variation in chemotherapy dosage in trial arms, as the IP arm received a higher total dose in two of the 3 studies that found a survival benefit associated with IP. This dosage variation might also account for differences in toxicity between the two arms. They also noted that the RCT with the most positive results did not analyse by intention-to-treat; however, the authors of this RCT reported an increased benefit to the intervention group when all data were included. The included studies did not consistently report catheter-related side-effects.

Survival (7 RCTs n=1,806).

The authors stated that 3 RCTs of cisplatin-based IP-containing chemotherapy versus cisplatin-based IV therapy reported statistically significant increases in median survival time in the IP groups of 8 months (n=546; HR 0.76, 95% CI: 0.61, 0.96, p=0.02), 11 months (n=462; RR 0.81, 95% CI: 0.65, 1.00, one-tailed p=0.05) and 15 months (n=415; RR 0.75, 95% CI: 0.58, 0.97, p=0.03). A meta-analysis of 6 RCTs (n=1,716) with a variety of cisplatin-based IP regimens found a 12% decrease in the risk of death in the IP group over the 5-year follow-up (RR 0.88, 95% CI: 0.81, 0.95), with no statistically significant heterogeneity.

Toxicity.

A variety of complications were reported during IP infusion. The most common was increased abdominal pressure or distension, which was worse in women of small stature or with many adhesions. The 3 larger RCTs (n=1,423) compared rates of grade 3 or 4 adverse events in the two groups. Events that were significantly more common in the intervention group in one or more of these RCTs were leucopenia, thrombocytopenia, neutropenia, fatigue, infection, and gastrointestinal, metabolic and neurological effects. Overall, an 11 to 20% increase in grade 3 abdominal pain was reported in the IP group (6 RCTs, n=1,806).

Catheter-related complications affected 10 to 34% of women in the IP group in 4 RCTs (n=680). Catheter-related complications, including infection, blockage, leakage and port access problems, were the main cause of 34% of discontinued IP treatments in one RCT (n=415). The most commonly-reported catheter-related complication was pain, which was reported by 17 to 50% of women (3 RCTs, n=544).

Quality of life.

Significantly lower quality-of-life scores were reported in the IP group at baseline and before the fourth and sixth cycles in one RCT (n=415). However, there was no difference between the groups at the 1-year follow-up. Women with the lowest quality-of-life scores at baseline were the least likely to complete IP therapy.

Authors’ conclusions

Cisplatin-based IP chemotherapy is associated with a significant survival benefit for women with optimally-debulked stage III epithelial ovarian cancer, compared with IV chemotherapy alone, but with an increase in short-term toxicity.

CRD commentary

The review objective and inclusion criteria were clear, although the outcomes of interest were not specified. The search appeared adequate, although the search terms were not reported and it was not stated whether the search was restricted by language or publication status. It is unclear whether steps were taken to minimise potential reviewer bias and error in the review process, such as having decisions made independently by more than one reviewer. Information about study quality was lacking (e.g. which studies used intention-to-treat analysis), as was information about the statistical methods used to conduct the meta-analysis and to assess statistical heterogeneity. The authors’ conclusions appear to be supported by the data presented, but the poor reporting of review methods and lack of information about the quality of the primary studies make it difficult to assess their reliability.

Implications of the review for practice and research

Practice: The authors stated that cisplatin-based IP chemotherapy improves survival for women with optimally
debulked stage III ovarian cancer but increases short-term toxicity. Improved tolerability may increase therapy completion rates and lead to further improvements in survival. The authors also provided guidance for the delivery of IP chemotherapy.

Research: The authors stated that future research should investigate IP techniques such as optimum catheter type, insertion technique and timing of insertion, and should investigate carboplatin-based IP regimens. Standards of practice should be developed for IP therapy, accompanied by monitoring of outcomes over time.

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