Should patients with ovarian cancer receive intraperitoneal chemotherapy following initial cytoreductive surgery?

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A novel intraperitoneal chemotherapy regimen, trialled in the GOG 172 study, represents a new standard of care for patients with optimally resected stage III ovarian cancer, but should be offered on an individualised basis.

Interest in the intraperitoneal delivery of chemotherapy to patients with ovarian cancer with minimal residual disease following initial cytoreductive surgery has been rekindled with the recent publication of a Gynecologic Oncology Group study, GOG 172. This study compared intravenous paclitaxel followed by intraperitoneal cisplatin and paclitaxel, or by intravenous cisplatin, in patients with stage III epithelial ovarian cancer (optimal cytoreduction). The authors reported a 15.9-month improvement in median overall survival in those patients who received intraperitoneal therapy. The National Cancer Institute (NCI) issued a bulletin suggesting that, in women with stage III epithelial ovarian cancer, consideration should be given to the administration of intraperitoneal cisplatin and a taxane.[1]

This study and two previous randomised trials demonstrated an improvement in overall survival with intraperitoneal cisplatin. Alberts et al.[2] performed a direct head-to-head comparison, whereas Markman et al.[3] added two additional cycles of high-dose carboplatin in the intraperitoneal arm. Although the prior studies did not result in an NCI alert or a change in clinical practice, the data in aggregate warrant consideration of first-line intraperitoneal therapy in this group of patients. Before one adopts the current regimen, several issues deserve consideration.

GOG 172 compares three drugs (two intraperitoneal and one intravenous) with two intravenously administered drugs and a different schedule. The intraperitoneal route results in a continuous infusion via the intraperitoneal and intravenous route. Only 42% of the intraperitoneal arm received the assigned intraperitoneal therapy, and 18% of patients assigned to intraperitoneal therapy received intravenous carboplatin and paclitaxel after discontinuation of intraperitoneal therapy because of toxicity. Toxicities resulting in discontinuation of the intraperitoneal therapy included problems related to the access device, abdominal pain with infusion, and intolerance to the higher doses of cisplatin. How the number of cycles of treatment affected survival is unknown.

When GOG 172 was designed, the results of GOG 158 were not available. GOG 158 reported an improvement in median overall survival of 8.7 months (relative risk 0.84; 95% CI 0.70–1.02) for patients treated with intravenous carboplatin and paclitaxel compared with those treated with intravenous cisplatin and paclitaxel.[4] Although cross-trial comparisons are not statistically valid and the populations may differ, it is interesting to compare the differences in

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outcome between the GOG 158 intravenous carboplatin plus paclitaxel arm and the GOG 172 intraperitoneal therapy arm. The difference in progression-free survival is 3.1 months and in overall survival 8.2 months between the two studies in favour of the intraperitoneal route. There are no differences in two-year survival rates, and only a 4–5% difference in four-year survival rates.

The results of this study and the previous phase III randomised trials[2,3] suggest that a new standard of care in chemotherapy has been reached in the primary chemotherapeutic management of small-volume residual advanced ovarian cancer; however, there remain a few hurdles to widespread acceptance. Until well-controlled, prospective randomised trials demonstrate a survival advantage over standard chemotherapy (intravenous carboplatin and paclitaxel, instead of intravenous cisplatin and paclitaxel, the control arm in GOG 172), intraperitoneal therapy need not be routinely administered to patients with optimal stage III disease. What practitioners should not do is make modifications to the regimen as published, as this might also modify the treatment's efficacy.

Details of the references cited in this article can be accessed at www.cancerworld.org/cancerworld

Synopsis

DK Armstrong, B Bundy, L Wenzel, et al. (2006) **Intraperitoneal cisplatin and paclitaxel in ovarian cancer.** *N Engl J Med 354:34–43*

Background. Surgery and standard intravenous chemotherapy with a platinum-taxane combination induces complete remission in the majority of patients with newly diagnosed ovarian cancer. Most patients will eventually relapse and die from their disease, however, despite escalation of the dose of intravenous chemotherapy. Although preclinical, clinical and pharmacokinetic data support the use of intraperitoneal therapy in ovarian cancer, this strategy has not been widely accepted.

Objective. To explore whether the use of intraperitoneal chemotherapy with cisplatin and paclitaxel improves progression-free and overall survival compared with intravenous cisplatin and paclitaxel in ovarian cancer.

Design. In this randomised, phase III study conducted by the Gynecologic Oncology Group, patients with stage III epithelial ovarian or peritoneal carcinoma who had not undergone previous chemotherapy or radiation were studied. Inclusion criteria were Gynecologic Oncology Group performance status 0–2 (where 0 was fully active and 4 completely disabled), residual mass following surgery limited to 1 cm in diameter, adequate hepatic and renal function, and normal blood counts.

Intervention. Between March 1998 and January 2001, participants were randomly assigned to receive six cycles of treatment with intravenous paclitaxel (135 mg/m^2) on day 1 followed by intravenous cisplatin (75 mg/m^2) on day 2 (intravenous therapy), or six cycles of intravenous paclitaxel (135 mg/m^2) on day 1 followed by intraperitoneal cisplatin (100 mg/m^2) on day 2 and intraperitoneal paclitaxel (60 mg/m^2) on day 8 (intraperitoneal therapy).

Outcome measures. Progression-free survival and overall survival were the primary endpoints, and toxicity and quality of life were also assessed.

Results. Median progression-free survival was 18.3 months in the intravenous therapy group and 23.8 months in the intraperitoneal therapy group (P=0.05). Median overall survival was 49.7 months in the intravenous therapy group and 65.6 months in the intraperitoneal therapy group (P=0.03). Compared with the intravenous therapy group, fewer patients in the intraperitoneal therapy group received all six cycles of the assigned treatment (42% vs 83%), and more patients had severe or life-threatening pain, fatigue or haematologic, metabolic, gastrointestinal, or neurologic toxicity (P<0.001). Catheter-related complications comprised the main reason for discontinuation of intraperitoneal treatment. After adjustment for baseline quality-of-life score, age and performance status, patients receiving intraperitoneal therapy had inferior quality of life before cycle 4 (P<0.001) and 3-6 weeks after treatment compared with patients receiving intravenous therapy, but there was no difference 1 year after treatment. Median duration of follow-up was 48.2 months in the intravenous therapy group and 52.6 months in the intraperitoneal therapy group.

Conclusion. Women with optimally debulked ovarian cancer receiving intraperitoneal therapy with cisplatin and paclitaxel following intravenous therapy with paclitaxel had a substantial reduction in the risk of death compared with women receiving intravenous paclitaxel plus cisplatin.

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