

Intraperitoneal Chemotherapy for Ovarian Cancer: Where Are We Now?

Pankaj Singhal, MD, and Shashikant Lele, MD, *Buffalo, New York*

Key Words

Ovarian carcinoma, intraperitoneal chemotherapy, intraperitoneal catheter, cisplatin, paclitaxel

Abstract

Patients with advanced epithelial ovarian cancer are conventionally treated with intravenous (IV) platinum- and taxane-based chemotherapy to try to eradicate residual disease after optimal cytoreductive surgery, resulting in a median overall survival of 49 months. The Gynecologic Oncology Group (GOG) conducted 3 large randomized, phase III clinical trials of intraperitoneal (IP) chemotherapy (GOG 104, 114, and 172) that clearly showed superior progression-free and overall survival with IP chemotherapy compared with IV chemotherapy. All 3 clinical trials investigated IP cisplatin, with the last one adding IP paclitaxel. The most recent study (GOG 172) resulted in a median survival of 66 months for patients in the IP arm versus 50 months for those in the IV arm. Fewer patients in the IP arm than in the IV arm completed all 6 treatment cycles (42% vs. 83%, respectively) because of the toxic effects of chemotherapy and IP catheter-related complications. Initially, patients in the IP arm reported significantly worse quality of life than those in the IV arm. However, at 12-month follow-up, the groups experienced no difference in quality of life, except that paresthesias were more likely to persist at moderate levels among patients in the IP arm. Based on these clinical trials, the National Cancer Institute issued a clinical announcement recommending that women with stage III ovarian cancer who undergo optimal surgical cytoreduction be considered for IP chemotherapy. (*JNCCN* 2006;4:941–946)

Background

Ovarian cancer is the leading cause of gynecologic cancer death in the United States.¹ Approximately 75% of patients with epithelial ovarian carcinoma have disseminated

peritoneal disease at diagnosis. Relapse rates approach more than 50% for patients experiencing complete pathologic response after primary cytoreductive surgery followed by frontline standard chemotherapy with an intravenous (IV) platinum agent combined with taxanes.^{2–5}

The rationale for intraperitoneal (IP) chemotherapy is that ovarian cancer remains confined primarily to the peritoneal cavity during most of its natural course. Furthermore, a longer half-life of the drug and a higher drug concentration directly at the tumor site are found in the peritoneal cavity, thereby reducing systemic toxicities associated with the higher doses needed with IV chemotherapy.^{6–8} Certain chemotherapeutic agents, including cisplatin and, more recently, paclitaxel, were found to have a distinct pharmacokinetic advantage when administered intraperitoneally. IP cisplatin and carboplatin were found to have a 10- to 20-fold, and paclitaxel more than a 1000-fold, greater exposure in the peritoneal cavity than these drugs administered intravenously.^{9–13}

Front-Line Intraperitoneal Chemotherapy

Over the past 2 decades, several phase III randomized clinical trials have compared IP chemotherapy with IV chemotherapy as front-line treatment for ovarian cancer.^{14–20} In all trials, chemotherapy was administered after completion of primary cytoreductive surgery (Table 1).

The Gynecologic Oncology Group (GOG) in collaboration with the Southwest Oncology Group (SWOG) conducted 3 large, multicenter, randomized, phase III clinical trials. Compelling evidence shows IP chemotherapy to be superior to standard IV chemotherapy in the primary chemotherapeutic management of small-volume, residual, advanced epithelial ovarian cancer.^{15,19,20} The most recent of these trials reported the most improvement in median survival (15.9 months) for patients with

From the Department of Gynecologic Oncology, Roswell Park Cancer Institute, Buffalo, New York.

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Correspondence: Shashikant Lele, MD, Department of Gynecologic Oncology, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263. E-mail: shashi.lele@roswellpark.org

Table 1 Randomized Trials Comparing Intravenous Versus Intraperitoneal First-Line Chemotherapy Treatment of Epithelial Ovarian Cancer

Study	Number of Patients	Control Arm (IV)	Experimental Arm (IP)	Eligibility Criteria	Median Duration of Survival (mo)			Treatment Hazard Ratio (IP vs. IV therapy)	
					Control Arm (IV)	Experimental Arm (IP)	P value	PFS	OS
GOG 104/ SWOG 8501 Alberts et al., ¹⁵ 1996	546	Cisplatin, 100 mg/m ² IV; Cyclophosphamide, 600 mg/m ² IV, q3wk × 6 cycles	Cisplatin, 100 mg/m ² IP; Cyclophosphamide, 600 mg/m ² IV, q3wk × 6 cycles	Stage III, ≤2 cm residual	41	49	0.02	NR	0.76 (95% CI, 0.34–1.00)
Polyzos et al., ¹⁶ 1999	90	Carboplatin, 350 mg/m ² IV; Cyclophosphamide, 600 mg/m ² IV, q3wk × 6 cycles	Cisplatin, 350 mg/m ² IP; Cyclophosphamide, 600 mg/m ² IV, q3wk × 6 cycles	Stage III	25	26	NS	NR	NR
Gadducci et al., ¹⁷ 2000	113	Cisplatin, 50 mg/m ² IV, Paclitaxel, 135 mg/m ² (24 h) IV, q4wk × 6 cycles	Cisplatin, 50 mg/m ² IP; Cyclophosphamide, 60 mg/m ² IV; Etoposide, 60 mg/m ² IV, q4wk × 6 cycles	Stage II–IV, < 2 cm residual	51	67	0.14	0.70	0.67
GOG 114/ SWOG 9227 Markman et al., ¹⁹ 2001	462	Cisplatin, 75 mg/m ² IV; Paclitaxel, 135 mg/m ² (24 h) IV, q3wk × 6 cycles	Carboplatin (AUC9) IV q28d × 2 cycles; Cisplatin, 100 mg/m ² IP; Paclitaxel, 135 mg/m ² (24 h) IV q3wk × 6 cycles	Stage III, ≤1 cm residual	52.2	63.3	0.05	0.78 (95% CI, 0.66–0.94)	0.81 (95% CI, 0.65–1.00)
GOG 172 Armstrong et al., ²⁰ 2006	415	Cisplatin, 75 mg/m ² IV; Paclitaxel, 135 mg/m ² (24 h) IV, q3wk × 6 cycles	Paclitaxel, 135 mg/m ² (24 h) IV q3wk × 6 cycles	Stage III, ≤1 cm residual	49.7	65.6	0.03	0.80 (95% CI, 0.64–1.00)	0.75 (95% CI, 0.58–0.97)

Abbreviations: AUC, area under the curve; CI, confidence interval; GOG, Gynecologic Oncology Group; IV, intravenous; IP, intraperitoneal; PFS, progression-free survival; OS, overall survival; SWOG, Southwest Oncology Group.

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advanced ovarian cancer.²⁰ In this study, Armstrong et al.²⁰ (GOG 172) compared IV and IP cisplatin and paclitaxel versus IV administration alone in front-line chemotherapy for stage III epithelial ovarian or primary peritoneal cancer with no residual mass greater than 1.0 cm in diameter after primary cytoreductive surgery. The experimental regimen consisted of IV paclitaxel, 135 mg/m², administered over 24 hours on day 1; IP cisplatin, 100 mg/m², on day 2; and IP paclitaxel, 60 mg/m², on day 8. The control arm in this study underwent the GOG standard treatment of IV infusion of paclitaxel, 135 mg/m², over 24 hours on day 1, and IV cisplatin, 75 mg/m², on day 2. The IP treatment resulted in a highly statistically significant improvement in both progression-free (median, 23.8 vs. 18.3 months; $P = .027$) and overall survival (median, 65.6 vs. 49.7 months; $P = .017$).

The IP arm was also associated with significantly more myelosuppression, emesis, neuropathy, and abdominal discomfort. However, secondary to these toxicities, only 48% of patients underwent 3 or fewer cycles of IP treatment, and 42% of patients were able to complete all 6 cycles of IP therapy. It is possible that if all the patients in the IP therapy group were able to complete the intended 6 cycles of treatment, the benefit would have been much greater.

The 2 previous intergroup GOG phase III randomized clinical trials with cisplatin-based IP therapy (GOG 104 and 114) also showed IP therapy to be superior to IV treatment.^{15,19} In the study by Alberts et al.¹⁵ (SWOG 8501/GOG 104), patients with small-volume disease (largest residual tumor nodule < 2 cm in maximum diameter) after surgical cytoreduction were randomly assigned to receive either IV or IP cisplatin (100 mg/m²). All patients also received IV cyclophosphamide (600 mg/m²). The IP experimental regimen was associated with a statistically significant improvement in overall survival (median, 49 vs. 41 months; $P = .02$).

However, the favorable results of GOG 104 were masked by another GOG clinical trial reporting significantly increased overall survival (median, 38 months with IV paclitaxel and cisplatin vs. 24 months with cyclophosphamide plus cisplatin) in patients with stage III ovarian cancer with minimal residual disease treated with front-line IV paclitaxel and cisplatin chemotherapy.² Therefore, IV paclitaxel and cisplatin became the standard component of ovarian cancer management.²

The hypothesis that administering IP cisplatin would produce additional clinical benefit beyond that achieved with an IV regimen of cisplatin and paclitaxel led to a second, large, randomized phase III clinical trial (GOG 114/SWOG 9227) comparing IV versus IP cisplatin-based front-line chemotherapy for small-volume (< 1 cm) residual ovarian cancer after primary surgical cytoreduction.¹⁹ All patients in this trial received IV paclitaxel in addition to either IV or IP cisplatin. The control arm of this study used the new standard regimen of IV cisplatin (75 mg/m²) plus paclitaxel (135 mg/m²) administered over 24 hours. The experimental arm used IP cisplatin (100 mg/m²) plus IV paclitaxel (135 mg/m²) administered over 24 hours. To maximize the benefit of IP treatment, chemical debulking was attempted by reducing the size of any residual tumor nodule to less than could be accomplished surgically. The patients in the IP arm were also treated with 2 cycles of IV carboplatin at a moderately high dose (area under the curve, 9) before IP therapy was initiated. Unfortunately, although chemical debulking was an interesting concept, administering carboplatin resulted in such severe bone marrow suppression that 19% of the patients in the study arm underwent 2 or fewer courses of the planned IP treatment, thereby bewildering the trial results.

However, GOG 114/SWOG 9227 showed that treatment with IP cisplatin therapy was associated with a statistically significant improvement in progression-free interval (27.9 months in the IP arm vs. 22.2 months in the IV arm; $P = .01$) and a borderline significant improvement in overall survival (63.2 months in the IP arm vs. 52.2 months in the IV arm; $P = .05$). Notably, several randomized phase III clinical trials failed to show any benefit of platinum dose-intensity at drug concentrations that are safely attainable with systemic drug delivery.^{21–25} The favorable survival data from the GOG 114/SWOG 9227 study further emphasize the benefit of IP cisplatin drug delivery in ovarian cancer.

Toxicity and Quality of Life Associated with IP Chemotherapy

IP chemotherapy is discontinued prematurely for several reasons that can be broadly divided into complications associated with an IP catheter, toxicities associated with IP administration, and toxicities associated with the chemotherapy itself.

Alberts et al.¹⁵ (GOG 104/SWOG 8501) reported that patients undergoing IP therapy experienced a lower incidence of neutropenia, tinnitus, and neuromuscular toxic effects but a significantly higher incidence of abdominal discomfort and pulmonary toxicities. Markman et al.¹⁹ (GOG 114/SWOG 9227) and Armstrong et al.²⁰ (GOG 172) reported significantly higher incidences of neutropenia, thrombocytopenia, gastrointestinal, metabolic, and neurologic toxicities in patients undergoing IP chemotherapy.

In the most recent GOG 172 study, investigators analyzed the reasons that prescribed courses of IP chemotherapy were prematurely discontinued in 119 patients.²⁶ Catheter-related complications were observed in 40 of 119 (33%) patients, including 21 with catheter infection, 9 with catheter blockade, 3 with catheter leakage, 5 with access problems, and 1 with vaginal leakage. Patients who underwent a left colonic or rectosigmoid resection were less likely to receive all planned doses of IP therapy because of catheter-related complications. When compared with fenestrated catheters with Dacron cuffs, fully implantable ports attached to a single-lumen venous silicone catheter appeared to be associated with less risk for inflow obstructions, bowel erosion, adhesion, and obstructions.²⁶

IP chemotherapy was also discontinued in 4 patients with abdominal pain potentially related to the presence of an IP catheter, 4 patients with bowel complications, and 19 patients who refused further IP therapy. Non-catheter-related reasons for discontinuation (29%) included nausea, vomiting, dehydration, and renal/metabolic complications.

GOG 172 also included a formal quality-of-life analysis, and patients undergoing IP therapy reported statistically significant worse quality of life before cycle 4 and at 3 to 6 weeks after treatment than those in the systemic drug delivery arm. However, at 12-month follow-up, no difference in quality of life was seen between the 2 treatment groups, except that paresthesias were more likely to persist at moderate levels among patients in the IP chemotherapy arm.^{27,28} These findings suggest that most of the additional toxicity with IP delivery is generally transient. Furthermore, the neurologic toxicity experienced by patients in the IP arm was probably caused by the 33% higher dose of cisplatin administered compared with those in the IV arm (100 mg/m² vs. 75 mg/m²).

Where Are We Now?

Although these large trials clearly show that IP administration of chemotherapy confers a significant survival benefit among women with optimally-cytoreduced epithelial ovarian cancer compared with IV administration alone, several unanswered questions still exist.

For example, the optimal number of IP treatment cycles for women whose ovarian cancer has been surgically cytoreduced to less than a 1-cm residual tumor remains unclear. IP treatments in GOG 104, 114, and 172 were limited because of toxicities, and patients received 58%, 71%, and 42% of the optimal rates, respectively (Table 2).^{15,19,20}

No randomized studies address whether IP chemotherapy would also benefit patients who undergo suboptimal cytoreductive surgery followed by standard courses of IV chemotherapy with resultant minimal residual disease. Furthermore, no studies of IP chemotherapy in women with stage IV ovarian cancer who underwent optimal cytoreductive surgery have been reported. Piccart et al.²⁹ reported a survival benefit with consolidation IP chemotherapy among women without clinical evidence of disease after primary surgery and platinum-based chemotherapy. IP chemotherapy as a consolidation therapy is currently not recommended because of the lack of well-controlled randomized clinical trials.

Almost half of patients in GOG 172 underwent only 3 or fewer IP chemotherapy courses, often because of catheter-related complications.²⁶ No studies have compared techniques for placing IP catheters, types of catheters, timing of placement relative to primary surgery with bowel resection, and techniques for IP administration of chemotherapy in patients with ovarian cancer.

Table 2 Percent Completion Rate of Intraperitoneal Chemotherapy

Study	IV Regimen, (%)	IP Regimen (%)
GOG 104 & SWOG 8501 Alberts et al., ¹⁵ 1996	58	58
GOG 114 & SWOG 9227 Markman et al., ¹⁹ 2001	86	71
Gadducci et al., ¹⁷ 2000	96	65
GOG 172 Armstrong et al., ²⁰ 2006	90	42

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Summary

Two decades of research in IP chemotherapy has shown significant survival benefit with this technique and its feasibility in clinical practice. Patients who benefit most from IP chemotherapy are those who have undergone optimal cytoreductive surgery (residual tumors < 1 cm), emphasizing the critical role of effective surgical debulking in patients with advanced ovarian cancer. Peritoneal catheters with fenestrations and Dacron cuffs, which were used in the past, should be avoided; a single-lumen, semipermanent subcutaneous venous access port connected to a single-lumen venous catheter is preferred.^{26,30,31}

Recommendations for a precise IP chemotherapy regimen are not possible because the IP chemotherapy regimens used in published clinical trials were modified based on patient tolerance. Increased toxicities associated with IP chemotherapy warrant careful monitoring and treatment modifications, along with the use of contemporary supportive care measures or newer drugs with fewer toxicities. Generally, the toxicities associated with IP chemotherapy are short-term and manageable.

In conclusion, many questions remain regarding optimal IP chemotherapy cycles, catheter placement, timing, type of catheter, and overall treatment for women with small-volume, residual, and advanced ovarian cancer. Although IP chemotherapy delivery is complex, requiring modification of existing treatment strategies and the development of new skills, the benefit of IP chemotherapy is unquestionable.

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