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Factors associated with improved toxicity and tolerability of intraperitoneal chemotherapy in advanced-stage epithelial ovarian cancers

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OBJECTIVE: We sought to evaluate the toxicity and tolerability of the intraperitoneal/intravenous regimen by comparing the modified regimen that is used at the Moffitt Cancer Center vs the published findings of the Gynecologic Oncology Group Study 172.

STUDY DESIGN: Using the Moffitt database, we evaluated the outcomes of patients who underwent primary optimal cytoreduction for stage IIC-IV epithelial ovarian, tubal, and peritoneal carcinoma followed by the intent-to-treat with intraperitoneal/intravenous chemotherapy. National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) was used to grade adverse events.

RESULTS: We analyzed patient data from 2006-2011 and identified 69 patients who met our inclusion criteria. The most frequent grade 3/4 toxicities were neutropenia (48%), gastrointestinal (9%), metabolic (9%), and infection (5%). Remaining toxicities occurred in <5% of patients. Patients received a greater number of cycles compared with the Gynecologic Oncology Group Study 172 (4.28 vs 3.66, respectively; $P = .0088$).

CONCLUSION: With the use of supportive care and the preemptive management of established side-effects, the associated toxicities and tolerability of intraperitoneal chemotherapy can be improved.

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Background and Objective

Ovarian cancer is the leading cause of death among patients with gynecologic malignancies. Lacking a screening method, most patients present with advanced (stage III/IV) disease, resulting in a Surveillance, Epidemiology and End Results Program–reported 5-year survival rate of 44%.

In 2006, the Gynecologic Oncology Group (GOG) published the results of a phase III randomized control trial (Study 172) comparing combined intraperitoneal/intravenous chemotherapy with standard intravenous chemotherapy. This study demonstrated a 6-month progression-free survival and a 16-month overall survival benefit in patients who were assigned randomly to intraperitoneal/intravenous therapy compared with intravenous therapy, which makes it a highly significant chemotherapy advance for epithelial ovarian cancer (EOC). Despite a high level of evidence on the survival benefit of intraperitoneal/intravenous therapy, barriers to its standard use include inconvenience, toxicity, poor tolerability, and port-related complications.

We hypothesized that the proactive management of documented side-effects and the addition of supportive care to a modified intraperitoneal/intravenous regimen would result in improved tolerability and toxicity.

Materials and Methods

This single-institution retrospective study of patients who received treatment at the

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Moffitt Cancer Center from January 2006 through December 2011 included patients who had undergone primary optimal cytoreductive surgery (no residual disease ≥1 cm) with a final pathologic diagnosis of stage IIC-IV EOC. From our database, we extracted eligible patients by identifying those who had been diagnosed with an ovarian, peritoneal, or fallopian tube malignancy who had received placement of an intraperitoneal port. According to our regimen, treatment on day 1 includes intravenous paclitaxel 135 mg/m^2 over 24 hours; treatment on day 2 includes intraperitoneal cisplatin 75 mg/m^2; and treatment on day 8 includes intraperitoneal paclitaxel 60 mg/m^2, repeated every 21 days for a goal of 6 cycles. The protocol was standardized to include supportive agents (Table). The National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0) was used to identify grade 3 and 4 toxicities that are consistent with the grading used in the GOG 172. A survival analysis was not performed.

Results

We identified 69 patients with stage IIC-IV optimally cytoreduced EOC who underwent placement of an Intraperitoneal port from 2006-2011. Most of our population had high-grade stage III serous adenocarcinoma of the ovary.

Neutropenia (48%), gastrointestinal (9%), metabolic (9%), and infectious (5%) toxicity were the most common grade 3/4 toxicities that occurred with our modified regimen. The differences in neutropenia and gastrointestinal, metabolic, and infectious toxicities were statistically significant as compared with the GOG 172 ($P < .0001$-$.0202$). There were no treatment-related deaths.

At Moffitt Cancer Center, 83% of patients were able to receive at least 3 cycles and 63% of patients were able to tolerate at least 5 cycles of intraperitoneal/intravenous vs 64% and 51%, respectively, in the GOG 172. Overall, patients at Moffitt received more cycles than those in the GOG 172 (4.28 vs 3.66 cycles; $P = .0088$). We identified 13 patients (19%) who experienced port-related complications.

TABLE
Supportive agents in the H. Lee Moffitt Cancer Center and Research Institute intraperitoneal/intravenous chemotherapy protocol

Day	Regimen
1: Before paclitaxel (intravenously)	1. Dexamethasone 20 mg in 100 mL normal saline solution intravenous piggy-back over 30 minutes
	2. Ranitidine 50 mg in 5% dextrose in 1/2 normal saline solution intravenous piggy-back over 15 minutes
	3. Lorazepam 0.5 mg intravenously/orally 30 minutes before chemotherapy
	4. Diphenhydramine 50 mg intravenously over 2-5 minutes OR chlorpheniramine 4 mg orally 30 minutes before chemotherapy
	5. 1000 mL 5% dextrose in 1/2 normal saline solution + 20 mEq potassium chloride + 2 g magnesium + 25 g mannitol @ 500 mL/hour starting 2 hours before completion of paclitaxel infusion (before cisplatin hydration).
2: Before cisplatin (intraperitoneally)	1. Aprepitant 125 mg orally 60 minutes before amifostine and 80 mg orally every 24 hours on days 3 and 4
	2. Dexamethasone 12 mg in 100 mL normal saline solution intravenous piggy-back over 30 minutes at 60 minutes before amifostine
	3. Odansetron 16 mg orally 60 minutes before amifostine
	4. Ranitidine 50 mg in 50 mL 1/2 normal saline solution intravenous piggy-back over 15 minutes at 60 minutes before amifostine
	5. Lorazepam 1 mg intravenously × 1 before amifostine
	6. Diphenhydramine or chlorpheniramine (see day 1)
	7. Amifostine (910 mg/m^2) in 50 mL normal saline solution intravenous piggy-back over 5 minutes at 30 minutes before cisplatin
	8. Warmed (37°C) normal saline solution 500 mL intraperitoneal rapid infusion (before and after cisplatin)
8: Before paclitaxel (intraperitoneally)	1. 1000 mL 5% dextrose in 1/2 normal saline solution + 20 mEq potassium chloride at 500 mL/hr
	2. Ranitidine 50 mg in 5% dextrose in 1/2 normal saline solution intravenous piggy-back over 15 minutes before chemotherapy
	3. Diphenhydramine or chlorpheniramine (see day 1)
	4. Dexamethasone 20 mg in 100 mL normal saline solution intravenous piggy-back over 30 minutes before chemotherapy
	5. Warmed (37°C) normal saline solution 500 mL intraperitoneal rapid infusion (before and after paclitaxel)
Additional	Pegfilgrastim subcutaneously 24-48 hours after completion of chemotherapy
	Prochlorperazine 10 mg intravenously/orally every 6 hours as needed for nausea/vomiting

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Comment

Intraperitoneal/intravenous chemotherapy for the treatment of advanced-stage EOC has the best-demonstrated overall survival rate for women with optimally cytoreduced stage III cancer. Our data support the feasibility of this regimen as a standard treatment.

At our institution, we aimed to deviate as little as possible from GOG 172 dosing and schedule to minimize impact on the benefit that was seen in that study. We offer

intraperitoneal chemotherapy as the preferred treatment to all patients with optimally debulked EOC if they have a GOG performance <2 and no preexisting grade 2 medical comorbidities.

Although we standardized several components of supportive care, our greatest modification to the GOG 172 regimen was a dose reduction of day 2 cisplatin (75 mg/m^2 vs 100 mg/m^2, respectively). Our modified regimen demonstrated a reduction in all recorded toxicities vs GOG 172.

Fever, infection, and leukopenia are well-documented toxicities that are associated with intraperitoneal chemotherapy. Supportive additions to our regimen include the standardized use of amifostine and granulocyte-colony stimulating factor.

With the proactive administration of these agents, we report improved rates of neutropenia (48% vs 76%, respectively) and infection (5% vs 16%, respectively) compared with the GOG 172. After neutropenia, gastrointestinal toxicity (grade 3/4) was the second most common grade 3/4 toxicity reported in the GOG 172, which occurred in 46% of patients. We suspect that the standardized preemptive administration of scheduled antiemetics (odansetron, dexamethasone, and aprepitant) and of as-needed antiemetics (prochlorperazine or metoclopramide), prewarming of intraperitoneal fluids, and ample intravenous hydration contributed to our decreased frequency of gastrointestinal (9%) and other toxicities. The most common subjective toxicity reported in the GOG 172 was neuropathy, which occurred in approximately twice the number of patients (19%) who were assigned randomly to the intraperitoneal/intravenous arm compared with the intravenous arm.

Poor tolerability or treatment completion rate has been an additional factor that has prevented the widespread acceptance of intraperitoneal/intravenous chemotherapy. Of patients in our cohort who received at least 1 dose of intraperitoneal chemotherapy, 83% were able receive at least 3 cycles of treatment vs 64% in the GOG 172. In addition, 63% of our patients received at least 5 cycles vs 51% in the GOG 172.

Intraperitoneal catheter-related complications remain a common cause of treatment morbidity and ultimately regimen discontinuation. Of the 13 patients (19%) in our study who had a port-related complication, 5 lost port access; 3 experienced a port infection; 3 had localized pain, and 2 had a small bowel obstruction. Our complication rates are similar to previously reported data.

When the GOG 172 protocol is followed, inconvenience remains an issue. Although logistics and convenience may have prevented several patients from opting to receive intraperitoneal chemotherapy on initiation, no patient discontinued treatment for those reasons.

To maximize the impact of intraperitoneal chemotherapy in the management of EOCs, we must continue to investigate ways to improve administration and treatment completion rates and reduce toxicities while maintaining efficacy. Modified intraperitoneal/intravenous regimens may be considered when toxicity and completion rates appear to have improved.

Reducing day 2 cisplatin and adding aggressive supportive care, which includes the routine use of a granulocyte-colony stimulating factor, amifostine, and antiemetics, makes the toxicity and tolerability of intraperitoneal chemotherapy reasonable.

CLINICAL IMPLICATIONS

- Treatment toxicity that is associated with intraperitoneal chemotherapy is best managed preemptively.
- Intraperitoneal/intravenous chemotherapy should be offered as a standard option to women with optimally debulked stage III epithelial ovarian cancer.
- Future studies should continue to investigate ways to improve the administration and reduce toxicity while maintaining efficacy. ■