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.

Key words: intraperitoneal chemotherapy, ovarian cancer, toxicity

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Ovarian cancer is the leading cause of death among patients with gynecologic malignancies.[1] Epithelial ovarian cancers (EOC) comprise 95% of ovarian malignancies and commonly are grouped together with peritoneal and fallopian tube cancer, which share a similar clinical course and response to treatment. Without a method of screening, most patients unfortunately will have advanced (stage III/IV) disease, which results in a Surveillance, Epidemiology and End Results Program–reported 5-year survival rate of 44%.[2] Although primary cytoreductive surgery followed by 6 cycles of taxane- and platinum-based chemotherapy is a well-established treatment, the optimal route, dose, and schedule are areas of ongoing discussion and investigation.

In 2006, the Gynecologic Oncology Group (GOG) published the results of a phase III randomized control trial (Study 172) that compared 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,[3] which makes it a highly significant chemotherapy advance for EOC. An article that was published in 2011 included the GOG 172 and 5 additional "high-quality studies" demonstrated a similar survival benefit, which further supports the use of intraperitoneal/intravenous chemotherapy for the treatment of EOC.[4]

Despite this high level of evidence in regard to survival benefit, the inconvenience, toxicities, tolerability, and port-related complications have been cited as barriers to the standard use of intraperitoneal/intravenous chemotherapy.[4,5] In an effort to reduce the negative factors that are associated with intraperitoneal/intravenous chemotherapy, several institutions have modified the regimen that originally was described in the GOG 172.[5,6]

At our institution (H. Lee Moffitt Cancer Center and Research Institute [MCC]), intraperitoneal chemotherapy is administered as published in the GOG 172 but with a reduced intraperitoneal cisplatin dose (75 mg/m^2 vs 100 mg/m^2). In addition, our institution incorporates a standardized set of supportive and prophylactic medications that include multidrug anti-emetics, amifostine, anxiolytics, and growth factors. Because a survival benefit of intraperitoneal/intravenous chemotherapy has been demon-

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TABLE 1
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/h
	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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strated in randomized controlled trials and supported by retrospective cohort studies, our primary objective was to investigate the tolerability and toxicities of our institution's approach vs those shown in previously reported data. We hypothesized that the proactive management of documented side-effects and the addition of supportive care to a modified intraperitoneal/intravenous regimen will result in improved tolerability and toxicity.

Materials and Methods

This single-institution, retrospective study received approval from the Institutional Review Board at the University of South Florida. Eligible patients received treatment at the MCC from January 2006 through December 2011. The patients who were included in the study had undergone primary optimal cytoreductive surgery (no residual disease ≥1 cm) with a final pathologic diagnosis of stage IIC-IV EOC. Patients were counseled on the known risks and benefits of intraperitoneal/intravenous vs standard intravenous chemotherapy either before or after surgery and had elected to receive intraperitoneal/intravenous chemotherapy.

Our study group was identified through queries within our internal cancer registry of patients who received care at our institution. The Moffitt Cancer Registry maintains a comprehensive dataset for patients who are diagnosed and/or treated for cancer at MCC. The data are reported to the Florida State Cancer Registry and the National Cancer Database. 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. All operative reports, progress notes, and laboratory data were reviewed from the time of initial evaluation to the completion of primary adjuvant treatment.

Our regimen follows: day 1 is intravenous paclitaxel 135 mg/m^2 over 24 hours; day 2 is intraperitoneal cisplatin 75 mg/m^2; and day 8 is intraperitoneal paclitaxel 60 mg/m^2, repeated every 21 days for a goal of 6 cycles. Additionally, the protocol was standardized to include the supportive agents shown in Table 1. After treatment initiation, there was not a rigid algorithm for the management of toxicities, which provided the gynecologic oncologist the discretion of when dose-delay, dose-reduction, or discontinuation of therapy was warranted.

The National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) was used to identify grade 3 and 4 toxicities (which is consistent with the grading used in the GOG

172). Recorded toxicities included bone marrow, gastrointestinal, renal, metabolic, and infectious. Catheter-related complications were also noted. Subjective toxicities were recorded but not included in our statistical analysis. A survival analysis was not performed. Descriptive statistics were considered with the use of frequency tables. To compare results from the GOG and MCC groups vs other variables, we used the χ^2 test with the exact method with Monte Carlo estimation. All probability values that are listed were 2-sided and considered significant at .05. Statistical analyses were performed with SAS software (version 9.3; SAS Institute Inc, Cary, NC).

Results

We identified 69 patients with stage IIC-IV optimally cytoreduced EOC who underwent placement of an intraperitoneal port from 2006-2011. Patient demographics and tumor characteristics are shown in Table 2. The median age at the time of diagnosis was 56 years (range, 31−87 years). Most of our population had high-grade stage III serous adenocarcinoma of ovarian primary. Four patients (6%) had stage IIC disease, and 1 patient (1%) had stage IV disease. Surgical cytoreduction was complete (no gross residual) in 42 patients (61%) and optimal (<1 cm residual) in 27 patients (39%).

Treatment toxicities among patients who received at least 1 cycle of intraperitoneal chemotherapy (n = 65) are reported in Figure 1. In Figure 2, we compare our toxicity rates with those reported in the GOG 172. Neutropenia (48%), gastrointestinal (9%), metabolic (9%), and infectious (5%) toxicities were the most common grade 3/4 toxicities that occurred with our modified regimen. The differences in neutropenia, gastrointestinal, metabolic and infectious toxicities, as compared with the GOG 172, were statistically significant ($P < .0001$-$.0202$). Thrombocytopenia had borderline significance ($P = .0535$). There were no treatment-related deaths.

Figure 3 shows the patients who received at least 1 cycle of intraperitoneal/intravenous chemotherapy and the proportion of those patients who were able to complete cycles 1-6 of the planned 6-cycle treatment. At MCC, 83% of patients were able to receive at least 3 cycles; 63% of patients were able to tolerate at least 5 cycles of intraperitoneal/intravenous (compared with 64% and 51%, respectively, in the GOG 172). Seventeen patients at MCC received their first cycle of chemotherapy intravenously because their intraperitoneal port was not placed at time of initial surgery (maximum number of intraperitoneal cycles, 5). Overall, patients at MCC received a greater number of cycles than those in the GOG 172 (4.28 vs 3.66 cycles; $P = .0088$). There was no statistical difference ($P = .6173$) in the percentage of patients who did not receive intraperitoneal/intravenous chemotherapy, despite undergoing intraperitoneal port placement between the 2 studies (MCC, 6%; GOG 172, 8%). We identified 13 patients (19%) who experienced port-related complications, of which 8 complications (12%) resulted in discontinuation of the intraperitoneal/intravenous regimen.

Finally, Figure 4 reveals the average number of cycles over time. Although a greater number of patients received intraperitoneal/intravenous chemotherapy over time, there

TABLE 2
Tumor characteristics among patients in the Gynecologic Oncology Group Study 172[a] and at the H. Lee Moffitt Cancer Center and Research Institute

Tumor characteristic	Patients, n (%)		*P* value
	Gynecologic Oncology Group Study 172	H. Lee Moffitt Cancer Center and Research Institute	
Total patients	205	69	
Tumor stage			
IIC		4 (6)	
IIIA	All stage III	6 (9)	
IIIB		8 (12)	
IIIC		50 (73)	
IV		1 (1)	
Histologic subtype			.0249
Serous adenocarcinoma	158 (77)	45 (65)	
Endometrioid adenocarcinoma	17 (8)	5 (7)	
Clear cell carcinoma	11 (5)	3 (4)	
Mixed epithelial/other	19 (9)	16 (23)	
Histologic grade			
1	25 (12)	1 (1)	
2	72 (35)	0	
3	106 (52)	68 (99)	
Gross residual disease			.011
No	78 (38)	42 (61)	
Yes (<1 cm)	127 (62)	27 (39)	
Disease site			.0165
Ovarian	183 (87)	60 (87)	
Primary peritoneal	27 (13)	6 (9)	
Fallopian tube	0	3 (4)	

[a] Data obtained from Armstrong et al.[3]

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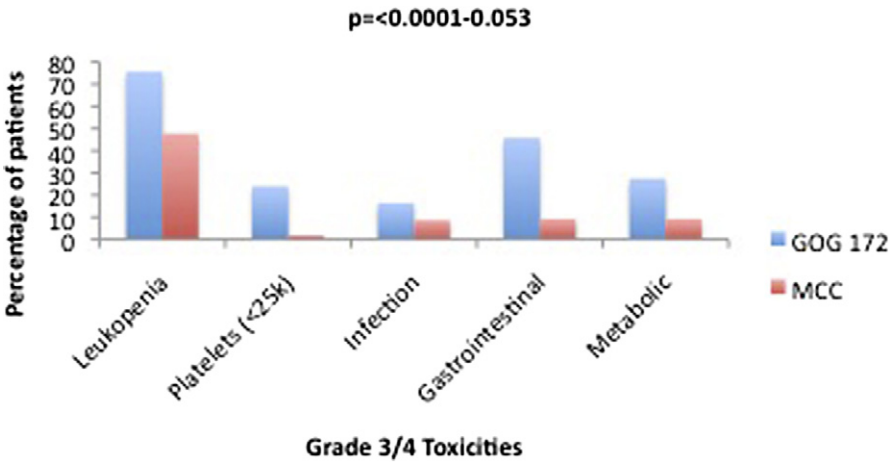
FIGURE 1
Regimen toxicity



Comparison of grade 3 or 4 toxicities among patients who received intraperitoneal/intravenous chemotherapy in the Gynecologic Oncology Group Study 172 (*GOG 172*)[3] and at the H. Lee Moffitt Cancer Center and Research Institute (*MCC*).

GI, gastrointestinal.

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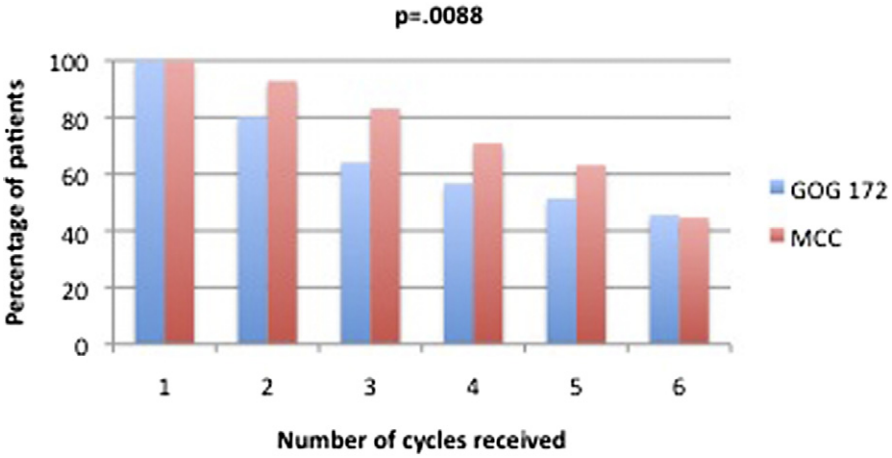
was no difference in number of cycles that were received ($P = .86$).

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. Treatment-associated toxicities, limited completion rate, port complications, and inconvenience of schedule have been reported as major obstacles or objections to offering this as standard therapy to patients. Our data support the feasibility of this regimen as a standard treatment. The toxicities and tolerability of this regimen are improved with a modest reduction of the initial cisplatin dosing and the preemptive management of anticipated side-effects.

FIGURE 2
Regimen tolerability



Progression through the intraperitoneal/intravenous chemotherapy regimen (maximum number of cycles, 6) in the Gynecologic Oncology Group Study 172 (*GOG 172*)[3] and at the H. Lee Moffitt Cancer Center and Research Institute (*MCC*).

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Since the release of the GOG 172, other physicians have developed modified treatment regimens in an attempt to minimize risks, improve convenience, and maintain efficacy. At our institution, we aimed to deviate as little as possible from the GOG 172 dosing and schedule to minimize any possible impact on the benefit 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. Unfortunately, we do not have the total number of eligible patients who did not opt for intraperitoneal chemotherapy. The population described in this report represents an intent-to-treat population, and the focus is on the ability to maximize tolerability once initiated.

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). This dosing has been accepted widely as a more appropriate dose and was used in the recently completed GOG Study 252.[7] Given the lack of demonstrable benefits of increasing platinum intensity for EOC, the impact is thought to be negligible. The possible benefit, other than improved short-term tolerability, is the possible reduction in long-term neuropathy.

Our modified regimen demonstrated a reduction in all recorded toxicities as compared with the GOG 172. With the exception of renal and thrombocytopenia toxicities, our results were statistically significant. Subjective toxicities were recorded for observational purposes solely, because analysis would be subject to reporting and proficiency biases.

Fever, infection, and leukopenia are well-documented toxicities that are associated with intraperitoneal chemotherapy. Here, we report improved rates of neutropenia (48% vs 76%) and infection (5% vs 16%) when compared with the GOG 172, respectively. Supportive additions to our regimen include the standardized use of amifostine and granulo-

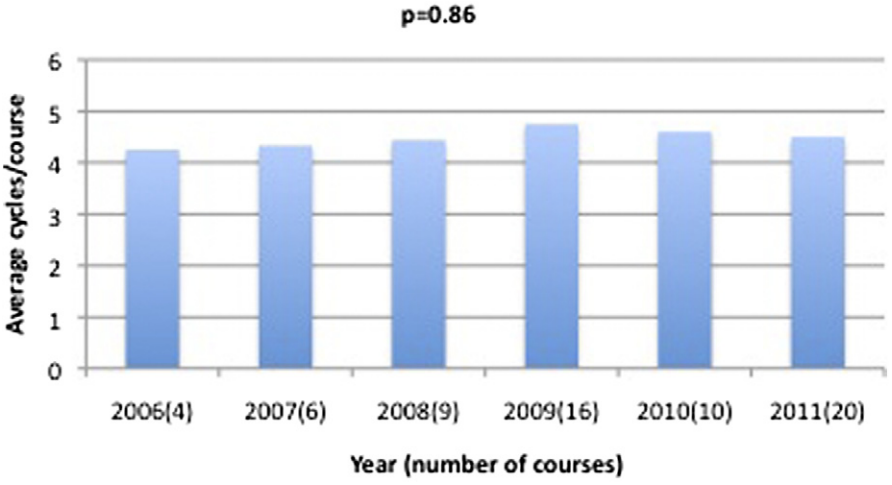
cyte-colony stimulating factor (GCSF). Amifostine has been shown to reduce hematologic, renal, and neurologic toxicities that are associated with cisplatin use.[8] In the GOG 172, the use of GCSF was used as a third-line reactive strategy after cycle delay and dose reduction for the management of leukopenia. With the proactive administration of these agents, we report improved rates of neutropenia (48% vs 76%) and infection (5% vs 16%) compared with the GOG 172. Similarly, these rates were reported at 12% and 2%, respectively, in a modified outpatient regimen described by Barlin et al.[5] In addition to a reduced dose of day-2 cisplatin (75 mg/m^2), their day-1 intravenous paclitaxel (135 mg/m^2) was administered over 3 hours (a 24-hour infusion in the GOG 172 and at our institution). This shorter infusion time for paclitaxel previously was associated with significantly less neutropenia when compared with the 24-hour regimen.[9] It is unclear whether and under what circumstances GCSF or amifostine was used within their modified outpatient regimen. Nevertheless, one concern for the use of the shorter infusion time is the increase in peripheral neuropathy that has been seen with this regimen. Because this was the one significant, persistent long-term toxicity that was seen in the GOG 172, we maintained the longer 24-hour infusion in our regimen.

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), 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. Given that this was the only significant difference to be identified in long-term toxicity between intraperitoneal/intravenous and intravenous, the goal in designing a treatment protocol is to minimize this potential toxicity. We identified 6 patients with grade 2 toxicity, and none with grade 3/4. We report one patient who was withdrawn from intraperitoneal therapy because of neurotoxicity, despite a diagnosis of grade 2. Although the interpretation may be limited by reporting bias, we suspect that a reduced day-2 cisplatin dose, the use of amifostine, and our reluctance to use a modified schedule of a short day-1 paclitaxel infusion would predict such a significantly reduced incidence of neuropathy.

Poor tolerability or treatment completion rate has been an additional factor that prevents the widespread acceptance of intraperitoneal/intravenous chemo-

FIGURE 3
Institutional tolerability



Comparison of the number of cycles of intraperitoneal/intravenous chemotherapy that were administered and the average number of cycles that were administered per course over time at the H. Lee Moffitt Cancer Center and Research Institute.

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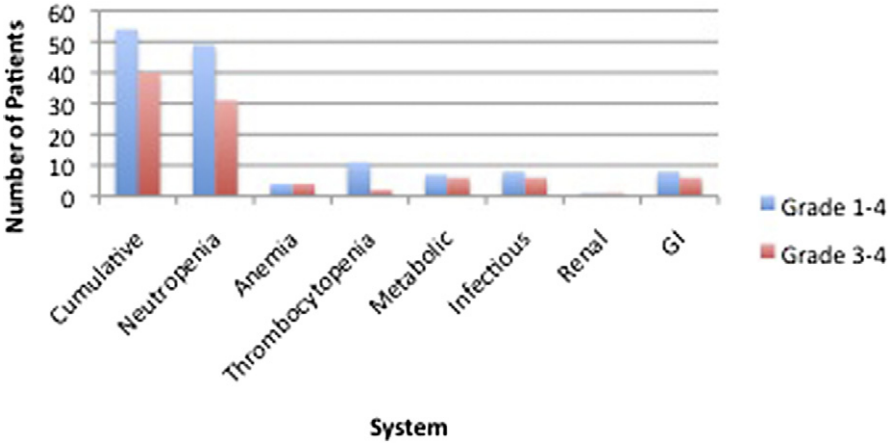
FIGURE 4
Institutional toxicity



Cumulative and individualized toxicities among patients who received intraperitoneal/intravenous chemotherapy at the H. Lee Moffitt Cancer Center and Research Institute (n = 65).

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therapy. Of patients in our cohort who received at least 1 dose of intraperitoneal chemotherapy, 83% were able receive at least 3 cycles of treatment compared with 64% in the GOG 172. Additionally, 63% of our patients received at least 5 cycles compared with 51% in the GOG 172. With such a high dropout rate after the first and second cycles, Armstrong et al[3] suggested that these initial cycles might have the most significant survival benefit. Yen et al[10] later indicated that at least 5 cycles should be administered to obtain a survival benefit. Our modified regimen and supportive management have demonstrated improved tolerance when compared with the GOG 172. When comparing our results over time, we demonstrated increasing numbers of patients who received intraperitoneal/intravenous chemotherapy from 2006-2011 (4 vs 20 patients), perhaps because of increasing regimen tolerability and familiarity among treating physicians. This familiarity over time, however, was not associated with increasing numbers of the intraperitoneal/intravenous cycles received per course. It is important to note that, in contrast to the GOG 172 (randomized), our patients were counseled on the known toxicities and ultimately were motivated to receive intraperitoneal/intravenous chemotherapy. This may have contributed to better patient selection and, thus, our improved tolerability and completion rates.

The use of intraperitoneal chemotherapy in the GOG 172 was limited to patients with stage III disease. In our study, we included patients with stage IIC-IV disease, because these patients are offered this regimen at our institution, in the appropriate setting. Stage IIC often has an aggressive clinical course with a 5-year survival similar to stage IIIA disease.[11] Our single patient with stage IV disease had an isolated subcutaneous implant, which, after primary debulking, was made optimal with only intraperitoneal disease remaining (<1 cm). We do not believe that the inclusion of these patients altered our toxicity and tolerability data.

Seventeen of our patients received their first cycle of chemotherapy intravenously; therefore, the maximum number of intraperitoneal cycles that were received was 5. This was done to prevent a delay in adjuvant treatment in those patients whose intraperitoneal catheter was not placed at their original surgery. Excluding these patients, we still report a greater number of patients receiving at least 5 cycles of intraperitoneal chemotherapy compared with results shown in the GOG 172 (58% vs 51%).

Left colon resection, which is often associated as a risk factor for failure to initiate intraperitoneal chemotherapy, was performed in 12 patients (17%).[12] Nine of these patients had the intraperitoneal port placed at the time of the initial surgery, and 7 patients received our modified intraperitoneal regimen as their first cycle. Our results do not support a correlation among patients who underwent left colon resection and our failure to initiate intraperitoneal chemotherapy.

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

Our complication rates are similar to previously reported data. In a follow-up article about intraperitoneal port outcomes in the GOG 172, port-related complications were noted to be the most common reason for treatment discontinuation. Of the 205 patients who were enrolled to the intraperitoneal arm, 40 patients (19.5%) discontinued intraperitoneal therapy primarily because of catheter complications.[12]

By following the GOG 172 protocol, inconvenience remains an issue. At our institution, patients often spend 36-48 hours in the hospital for the prechemotherapy visit, transfer to floor, initiation, and completion of both days 1 and 2 of the regimen. The modified outpatient regimen described by Barlin et al[5] provides an alternative with reasonable results in regard to toxicity profile, tolerability, and survival benefit. Although logistics and convenience may have prevented several patients from opting to receive intraperitoneal chemotherapy, on initiation, there were no treatment discontinuations for these reasons. With most literature arising from large cancer centers with facilities and educated teams that are capable of administering intraperitoneal chemotherapy, it is difficult to know the impact that the consideration of convenience has when making the decision between intraperitoneal/intravenous and intravenous chemotherapy.

An argument against the significance of the survival benefit seen in the intraperitoneal/intravenous arm of the GOG 172 is the unbalanced administration of paclitaxel. In 2009, the Japanese Gynecologic Oncology Group showed that, when combined with carboplatin, a regimen that consisted of a weekly dose-dense administration of paclitaxel had a survival benefit over the standard single-dose regimen (day 1 in a 21-day cycle).[13] Some researchers have suggested that this may have contributed to the survival benefit that was seen in the intraperitoneal arm of the GOG 172. The role of weekly, dose-dense paclitaxel is actively being investigated, both as a component of intraperitoneal and intravenous regimens.[7,14]

We decided to forego a survival analysis for patients who received intraperitoneal chemotherapy at our institution because the benefit has been well-established in a metaanalysis and in retrospective studies that have incorporated modified intraperitoneal regimens.[4,5] Additionally, the results of the recently completed the GOG 252, which includes the modified intraperitoneal regimen as 1 of 3 arms, should provide valuable survival data.[7]

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 as the toxicities, and completion rates appear improved. Risk factors for incomplete treatment (<5 cycles) should be emphasized during regimen selection (intravenous/intraperitoneal vs intravenous) to maximize survival benefit.

In conclusion, we have shown that, by a reduction of day-2 cisplatin combined

with aggressive supportive care that includes the routine use of a GCSF, amifostine, and antiemetics, the toxicity and tolerability of intraperitoneal chemotherapy are reasonable. Given the data that supports the clinical benefit of intraperitoneal/intravenous compared with intravenous for EOC, we are skeptical that there is a reasonable objection to offering the intraperitoneal/intravenous regimen as a standard option to eligible women.

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