



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

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### Abstract

**Objectives.** To evaluate the role of intraperitoneal (IP) chemotherapy as part of primary treatment in patients with advanced ovarian cancer and to develop standards of care within the context of current clinical practice.

**Methods.** A multidisciplinary expert panel, convened to develop standards on the use of IP chemotherapy, searched the MEDLINE, EMBASE, and Cochrane Library databases up to December 2006 for randomized trials or published standards on the efficacy and/or delivery of IP chemotherapy.

**Results.** Eight randomized trials comparing IP chemotherapy versus intravenous (IV) chemotherapy were identified. Three trials reported statistically significant improvements in median survival of 8.0, 11.0, and 15.9 months with cisplatin-based IP chemotherapy. In one trial, the 15.9-month improvement in median overall survival (RR=0.75, 95% CI=0.58–0.97) represented a 25% reduction in the risk of death with IP chemotherapy. Severe adverse events and catheter-related complications were often dose limiting with IP chemotherapy. Using a consensus-based approach with a nationally representative panel, multidisciplinary care standards were developed to review medical and surgical criteria, the practice setting, volume requirements, and the institutional criteria required to safely deliver IP chemotherapy.

**Conclusion.** The survival benefits with cisplatin-based IP chemotherapy may represent a significant improvement in the outlook for select patients with advanced ovarian cancer. The delivery of IP chemotherapy is more challenging than the IV route; however, severe adverse events and catheter-related complications may be offset through research defining the optimum treatment regimen, and the standardization of care. System-wide standards for the delivery of IP chemotherapy in Canada for patients with optimally debulked stage III ovarian cancer are offered.

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### Introduction

Epithelial ovarian carcinoma is the leading cause of death from gynecologic malignancies in the Western world. More than half of women with ovarian cancer present with advanced stage disease (FIGO III/IV) at the time of diagnosis [1]. Spread of the disease is

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often by local extension, by intra-abdominal dissemination to other sites within the peritoneal cavity, and by lymphatic spread to pelvic and para-aortic nodes in the retroperitoneum. Current best practice includes primary surgery by a gynecological oncologist for diagnosis, staging, and cytoreduction, followed by chemotherapy. There is good evidence to suggest that more comprehensive staging occurs and superior outcomes are achieved when gynecologic oncologists have been involved in ovarian cancer patients' surgery [2–4]. Unlike many other solid tumors, effective cytoreduction (debulking) conveys a survival benefit among women with ovarian carcinoma, thus the goal of primary surgery is to reduce the burden of ovarian cancer to no, or minimal, residual disease [5]. In clinical trials, as well as in clinical practice, the recent chemotherapeutic standard of care for patients post-surgery has been intravenous platinum and taxane-based chemotherapy [6,7].

As residual ovarian cancer after surgery and initial recurrences are primarily confined to the abdomen, intraperitoneal (IP) administration of chemotherapy, as a means of increasing the dose intensity delivered to the tumor, was first proposed several decades ago [8]. Certain chemotherapeutic agents, including cisplatin and, more recently, paclitaxel, were found to have distinct pharmacokinetic properties when given via an IP route [9,10]. They included a high IP concentration of drug, as well as a

longer half-life of the drug in the peritoneal cavity, compared to that observed with intravenous (IV) administration. For cisplatin there was a 10- to 20-fold greater exposure, and for paclitaxel a 1000-fold greater exposure in the peritoneal cavity over what is achievable with the IV route [11]. In addition, the IP administration resulted in prolonged systemic exposure to the chemotherapeutic agents leading to a slightly different toxicity profile.

The use of IP chemotherapy as part of primary treatment in optimally debulked patients with advanced ovarian cancer has evolved over the years, and has gained wider acceptance as new techniques and chemotherapy regimens have become available. In spite of the toxicity and catheter-related complications with cisplatin-based IP drug delivery; there is a growing willingness among clinicians and organizations to consider this route as a viable treatment option [12–18]. However, in terms of current clinical practice in Canada, this modality essentially represents a novel approach from a delivery of care point of view, one with great promise, but one also without a standardized system-wide model of care.

With the present gap in the Canadian capacity to deliver IP chemotherapy safely outside the setting of a clinical trial, the Society of Gynecologic Oncologists of Canada (GOC) set out to evaluate the existing evidence to determine the type of care and resources needed if IP chemotherapy were to be offered as part of

Table 1  
Literature search results and trial characteristics

Author, year (Ref) study identifier	IV chemotherapy (control regimen)	IP chemotherapy (experimental regimen)	Patient eligibility	Number of patients
Zylberberg et al. [19]	Doxorubicin 35 mg/m <sup>2</sup> IV Cisplatin 100 mg/m <sup>2</sup> IV Vinorelbine 10 mg/m <sup>2</sup> IV Bleomycin 15 mg/m <sup>2</sup> IV Fluorouracil 750 mg/m <sup>2</sup> IV Ifosfamide 1 g/m <sup>2</sup> IV Q 4 weeks × 10 cycles	Doxorubicin 20 mg/m <sup>2</sup> IV/30 mg/m <sup>2</sup> IP Cisplatin 50 mg/m <sup>2</sup> IV/50 mg/m <sup>2</sup> IP Vinorelbine 10 mg/m <sup>2</sup> IV Bleomycin 15 mg/m <sup>2</sup> IP Fluorouracil 500 mg/m <sup>2</sup> IV/500 mg/m <sup>2</sup> IP Ifosfamide 1 g/m <sup>2</sup> IV Q 4 weeks × 10 cycles	Stage III	20
Kirmani et al. [20]	Cisplatin 100 mg/m <sup>2</sup> IV Cyclophosphamide 600 mg/m <sup>2</sup> IV Q 3 weeks × 6 cycles	Cisplatin 200 mg/m <sup>2</sup> IP Etoposide 350 mg/m <sup>2</sup> IP Q 4 weeks × 6 cycles	Stages IIC–IV	62
Alberts et al. [21] SWOG 8501/GOG 104	Cisplatin 100 mg/m <sup>2</sup> IV Cyclophosphamide 600 mg/m <sup>2</sup> IV Q 3 weeks × 6 cycles	Cisplatin 100 mg/m <sup>2</sup> IP Cyclophosphamide 600 mg/m <sup>2</sup> IV Q 3 weeks × 6 cycles	Stage III ≤ 2 cm residual	546
Polyzos et al. [22] Greek	Carboplatin 350 mg/m <sup>2</sup> IV Cyclophosphamide 600 mg/m <sup>2</sup> IV Q 3 weeks × 6 cycles	Carboplatin 350 mg/m <sup>2</sup> IP Cyclophosphamide 600 mg/m <sup>2</sup> IV Q 3 weeks × 6 cycles	Stage III	90
Gadducci et al. [23] GONO	Cisplatin 50 mg/m <sup>2</sup> IV Cyclophosphamide 600 mg/m <sup>2</sup> IV Epidoxorubicin 60 mg/m <sup>2</sup> IV Q 4 weeks × 6 cycles	Cisplatin 50 mg/m <sup>2</sup> IP Cyclophosphamide 600 mg/m <sup>2</sup> IV Epidoxorubicin 60 mg/m <sup>2</sup> IV Q 4 weeks × 6 cycles	Stages II–IV < 2 cm residual	113
Yen et al. [24] Taiwan	Cyclophosphamide 500 mg/m <sup>2</sup> IV Cisplatin 50 mg/m <sup>2</sup> IV Q 3 weeks × 6 cycles	Cyclophosphamide 500 mg/m <sup>2</sup> IV Cisplatin 100 mg/m <sup>2</sup> IP Q 3 weeks × 6 cycles	Stage III 1 cm residual	118
Markman et al. [25] GOG 114/SWOG 9227	Cisplatin 75 mg/m <sup>2</sup> IV Paclitaxel 135 mg/m <sup>2</sup> (24 h) IV Q 3 weeks × 6 cycles	Carboplatin (AUC 9) IV q 28 days × 2 Cisplatin 100 mg/m <sup>2</sup> IP Paclitaxel 135 mg/m <sup>2</sup> (24 h) IV Q 3 weeks × 6 cycles	Stage III ≤ 1 cm residual	462
Armstrong et al. [26] GOG 172	Cisplatin 75 mg/m <sup>2</sup> IV Paclitaxel 135 mg/m <sup>2</sup> (24 h) IV Q 3 weeks × 6 cycles	Paclitaxel 135 mg/m <sup>2</sup> (24 h) IV Cisplatin 100 mg/m <sup>2</sup> IP Paclitaxel 60 mg/m <sup>2</sup> IP on day 8 Q 3 weeks × 6 cycles	Stage III ≤ 1 cm residual	415

Note. Ref, reference; IV, intravenous; IP, intraperitoneal; AUC, area under the curve; Q, every; GOG, Gynecologic Oncology Group, SWOG, Southwest Oncology Group, GONO, Gruppo Oncologico Nord Ovest.

clinical practice. As part of the process, it was understood that guidance on the delivery of IP chemotherapy represents an evolving paradigm, one that requires built-in quality assurance and dissemination processes that are adaptable to new and evolving practices. Standards for safe implementation of IP chemotherapy as well as mechanisms for the identification, management, and reporting of toxicity were important components to be considered as part of the endeavor to modify practice.

## Methods

As a primary objective, the GOC assembled an expert panel to review the evidence around IP chemotherapy as part of primary therapy for patients with advanced ovarian cancer. The secondary objective, if warranted, was to develop comprehensive multidisciplinary clinical care standards for the delivery of IP chemotherapy in the context of clinical practice in Canada. The expert panel comprised a nationally representative sample of gynecologic oncologists, medical oncologists, nurses, a pharmacist, and a methodologist (Appendix A). The process of systematic review and expert consensus was intended to promote an evidence-based approach for developing practice recommendations for care.

Through a series of consensus meetings, the evidence was reviewed and standards for the delivery of IP chemotherapy in Canada were established. The authors were editorially independent of any related funding sources. The executive of the GOC formally approves all guidance documents prior to public dissemination and a process for review and update has been established for this topic of interest.

The MEDLINE, EMBASE, and Cochrane Library databases were searched up to December 2006 for the standards on the delivery of IP chemotherapy and/or randomized controlled trials that compared patients with stage III epithelial ovarian cancer to primary treatment involving IP chemotherapy versus primary treatment with IV chemotherapy alone. Reference lists of related papers and recent review articles were also scanned for additional citations.

## Results

As seen in Table 1, eight randomized controlled trials, assessing IP chemotherapy versus IV chemotherapy for first-line treatment of ovarian cancer were identified [19–26]. No standards or guidance documents related to multidisciplinary clinical care standards for the delivery of IP chemotherapy were located. Across the randomized trials, IP chemotherapy was primarily cisplatin-containing and was delivered after primary surgery to patients whose disease was debulked to <1 cm [24–26], <2 cm [23] or <2 cm [21].

## Survival

Three trials [21,25,26] reporting statistically significant median survival advantages of 8.0, 11.0, and 15.9 months were detected with cisplatin-based IP-containing chemotherapy when compared with cisplatin-based IV chemotherapy alone (Table 2). The proportion of patients completing all of the planned cycles of IP chemotherapy in the three trials ranged from 42% to 71% [21,25,26]. In one trial, conducted by the Gynecologic Oncology Group (GOG), GOG 172, the combination of IP cisplatin and IP paclitaxel in the experimental arm resulted in a 15.9-month improvement in median overall survival (RR=0.75, 95% CI=0.58, 0.97) favoring the IP study arm [26]. The result represented a 25% reduction in the risk of death for patients treated with IP chemotherapy when compared with patients treated with IV chemotherapy.

Table 2  
Survival outcomes

Author, year (Ref) study identifier	Treatment groups	Number of patients	Median overall survival	Risk or hazard of death (values <1 indicate a survival benefit with IP chemotherapy)	Percent of patients who completed all cycles of chemotherapy
Zylberberg et al. [19]	IV chemotherapy	10	NR	NR	NR
	IP chemotherapy	10	NR		NR
Kirmani et al. [20]	IV chemotherapy	33	NR	NR	60%
	IP chemotherapy	29	NR		76%
			$p=0.45$		
Alberts et al. [21] SWOG 8501/GOG 104	IV chemotherapy	279	41.0 months		58%
	IP chemotherapy	267	49.0 months	HR 0.76 (0.61–0.96)	58%
			$p=0.02$		
Polyzos et al. [22] Greek	IV chemotherapy	46	25.0 months		NR
	IP chemotherapy	44	26.0 months	NR	NR
			$P=NS$		
Gadducci et al. [23] GONO	IV chemotherapy	56	51.0 months		96%
	IP chemotherapy	57	67.0 months	NR	64%
			$p=0.14$		
Yen et al. [24] Taiwan	IV chemotherapy	63	48.0 months		32%
	IP chemotherapy	55	43.0 months	HR 1.13 (0.69–1.86)	25%
			$p=0.47$		
Markman et al. [25] GOG 114/SWOG 9227	IV chemotherapy	227	52.2 months		86%
	IP chemotherapy	235	63.2 months	RR 0.81 (0.65–1.00)	71%
			$p=0.05^a$		
Armstrong et al. [26] GOG 172	IV chemotherapy	210	49.7 months		83%
	IP chemotherapy	205	65.6 months	RR 0.75 (0.58–0.97)	42%
			$p=0.03$		

Note. Ref, reference; IV, intravenous, IP, intraperitoneal; RR, relative risk; HR, hazard ratio; NR, not reported, GOG, Gynecologic Oncology Group; SWOG, Southwest Oncology Group; GONO, Gruppo Oncologico Nord Ovest.

<sup>a</sup> One-tailed study.

Table 3  
Complications occurring at the time of infusion and management recommendations

Problem	Cause(s)	Clinical manifestations	Interventions/Prevention/Management <sup>a</sup>
Abdominal distention or bloating/increase in abdominal pressure <sup>b</sup>	<ul style="list-style-type: none"> <li>• Large volume of fluid being instilled into the peritoneum<sup>c</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Pain during the infusion</li> <li>• Urinary frequency</li> <li>• Usually lasts 24–48 h</li> </ul>	<ul style="list-style-type: none"> <li>• Analgesia as ordered</li> <li>• Offer small, frequent meals</li> <li>• Raise head of bed to 30°</li> </ul>
Abdominal pain	<ul style="list-style-type: none"> <li>• Loculation of intraperitoneal fluid</li> <li>• Distension</li> </ul>	<ul style="list-style-type: none"> <li>• The chemotherapy infusion slows down</li> </ul>	<ul style="list-style-type: none"> <li>• Analgesia as ordered</li> <li>• Encourage patient to change position in bed to help distribute the fluid</li> <li>• Monitor intake and output</li> </ul>
Nausea and vomiting	<ul style="list-style-type: none"> <li>• Shift in fluid and electrolyte balance</li> <li>• Drug side effects</li> </ul>	<ul style="list-style-type: none"> <li>• Nausea and vomiting just after drugs are instilled</li> <li>• Lasts several hours after treatment</li> <li>• Delayed emesis 2 to 7 days post treatment</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor blood electrolytes and treat as necessary</li> <li>• Offer prolonged antiemetics</li> </ul>
Respiratory distress	<ul style="list-style-type: none"> <li>• Sudden rise in intra-abdominal pressure which restricts the diaphragmatic movement</li> </ul>	<ul style="list-style-type: none"> <li>• Shortness of breath (severe)</li> <li>• Dyspnea (severe)</li> </ul>	<ul style="list-style-type: none"> <li>• May require home hydration</li> <li>• During IP infusion raise the head of bed 30°</li> <li>• If severe shortness of breath develops: <ul style="list-style-type: none"> <li>• Stop chemotherapy</li> <li>• Rule out hypersensitivity</li> <li>• Prepare for the ABCs of resuscitation</li> <li>• Administer oxygen by mask at 35%, 10 l/min</li> <li>• Raise head of bed to 45°</li> <li>• Remain with patient and offer reassurance</li> </ul> </li> <li>• Offer extra blankets</li> </ul>
Chills (despite warmed IP fluid)	<ul style="list-style-type: none"> <li>• IP solution is cooler than body temperature</li> </ul>	<ul style="list-style-type: none"> <li>• Uncomfortable cold feeling</li> <li>• Shivering</li> </ul>	<ul style="list-style-type: none"> <li>• Offer hot drinks</li> </ul>
Catheter migration	<ul style="list-style-type: none"> <li>• Improper initial surgical placement of implanted port</li> </ul>	<ul style="list-style-type: none"> <li>• Excruciating pain</li> <li>• Respiratory distress</li> </ul>	<ul style="list-style-type: none"> <li>• Stop infusion</li> <li>• X-ray to locate catheter</li> <li>• Remain with patient and offer reassurance</li> <li>• Encourage oral intake of fluids</li> </ul>
Diarrhea	<ul style="list-style-type: none"> <li>• Increase in abdominal pressure</li> <li>• Drug side effect</li> </ul>	<ul style="list-style-type: none"> <li>• Frequent, loose watery bowel movements</li> <li>• Abdominal cramps</li> <li>• Generalized malaise</li> <li>• Electrolyte imbalance</li> </ul>	<ul style="list-style-type: none"> <li>• Antidiarrheal agents as prescribed</li> <li>• Monitor electrolytes and replace</li> </ul>
Extravasation at site of administration	<ul style="list-style-type: none"> <li>• Faulty catheter connection</li> <li>• Incorrect needle placement in implanted port</li> </ul>	<ul style="list-style-type: none"> <li>• Local pain</li> <li>• Swelling at the injection site</li> <li>• Chemotherapy leakage</li> </ul>	<ul style="list-style-type: none"> <li>• Ensure correct needle placement into the implanted port</li> <li>• Minimize patient movement during treatment (complete bed rest)</li> <li>• If extravasation occurs—stop the infusion and notify physician</li> <li>• Apply ice or heat to the site according to drug manufacturer's instructions</li> <li>• Strict aseptic technique with catheter (port) access/de-access</li> <li>• Obtain peritoneal cultures/Gram stain</li> </ul>
Bacterial peritonitis	<ul style="list-style-type: none"> <li>• Contamination from the skin</li> <li>• Contamination of the catheter (port)</li> <li>• Contamination from bowel</li> </ul>	<ul style="list-style-type: none"> <li>• Pain</li> <li>• Fever</li> <li>• Chills</li> <li>• Spasms</li> <li>• Labored respirations</li> <li>• Cloudy exudate</li> <li>• Nausea and vomiting</li> <li>• Severe abdominal pain during and following treatment</li> <li>• Fever</li> </ul>	<ul style="list-style-type: none"> <li>• Strict aseptic technique with catheter (port) access/de-access</li> <li>• Obtain peritoneal cultures/Gram stain</li> <li>• Local and systemic antibiotics as ordered</li> </ul>
Chemical peritonitis (inflammation) <sup>d</sup>		<ul style="list-style-type: none"> <li>• Chills</li> <li>• Diarrhea</li> </ul>	<ul style="list-style-type: none"> <li>• Double check dosage and dilution</li> <li>• Warm the solution prior to administering to the patient</li> <li>• Discontinue infusion if symptoms present and notify physician</li> <li>• Offer analgesia as ordered</li> </ul>

Table 3 (continued)

Problem	Cause(s)	Clinical manifestations	Interventions/Prevention/Management <sup>a</sup>
Electrolyte imbalance <sup>c</sup>	Shift in fluid and electrolyte balance	<ul style="list-style-type: none"> <li>• Changes in mental status</li> <li>• Tremors</li> <li>• Muscle twitching</li> <li>• Weakness</li> <li>• Ringing in ears</li> </ul>	<p>sodium thiosulfate, is recommended and have it available for physician to give</p> <ul style="list-style-type: none"> <li>• Stop infusion and notify physician</li> </ul>

Note. IV, intravenous; IP, intraperitoneal.

<sup>a</sup> The selection of appropriate patients and the subsequent patient education around IP chemotherapy are critical aspects for a successful IP chemotherapy program.

<sup>b</sup> Most common complaint.

<sup>c</sup> Worse in women of small stature or who have many adhesions.

<sup>d</sup> Not common with cisplatin or carboplatin.

<sup>e</sup> Not common unless the patient has some pre-existing fluid and electrolyte issues.

Six trials reported 5-year data sufficient for pooling results [20,21,23–26]. Despite patient and treatment modality differences, no statistically significant heterogeneity was detected across the trials. At 5 years, across the six trials, a 12% decrease in the risk of death was detected with IP chemotherapy when compared to IV chemotherapy (RR=0.88, 95% CI, 0.81–0.95).

There is still a debate as to whether it was the intraperitoneal component of chemotherapy that led to the improved survival outcomes, as total dose was altered in two of the three trials detecting survival differences [25,26]. The original GOG 114 trial however, only altered the route and not the dosing of chemotherapy with a consequent improvement in survival [21]. The consensus arrived at by the panel of Canadian experts was that despite lacking total clarity as to the contribution of the intraperitoneal component, the protocols, and all that they involved, there were significant gains in survival and therefore should be considered a reasonable treatment option for this patient population.

## Toxicity

Given the noted regimen disparity between the experimental and control arms of the randomized trials it is difficult to fully assess the impact of administering IP chemotherapy on toxicity. With the GOG 172 regimen [26] statistically significant differences in grade 3 or 4 adverse events with IP versus IV chemotherapy were detected for leucopenia (76% versus 64%), thrombocytopenia (12% versus 4%), infection (16% versus 6%), fatigue (18% versus 4%), metabolic (27% versus 7%), gastrointestinal (46% versus 24%) or neurological (19% versus 9%) side effects. In the GOG 114 trial [25], statistically significant differences in grade 3 or 4 adverse events were detected for neutropenia and thrombocytopenia, as well as for metabolic and gastrointestinal events with IP versus IV chemotherapy. In the GOG 104 trial [21], leucopenia, neutropenia, and neurotoxicity were significantly greater in the IP chemotherapy arm. Across the trials, where reported, an increase in abdominal pain ranging between 11% and 20% with grade III toxicity was reported [20–26].

The reporting of catheter-related complications was inconsistent across the trials. Four trials reported that catheter-related

complications ranged from  $\geq 10\%$  to 34% of patients who received IP chemotherapy [20,22,23,26]. In the GOG 172 trial [26], catheter-related complications were only reported for the 58% of patients who were unable to complete all of the planned cycles of IP chemotherapy. In that trial, the authors reported in a separate publication, that 34% of patients discontinued treatment primarily due to catheter-related complications including infection (21 patients), blockage (10 patients), leakage (3 patients) and port access problems (5 patients) [27]. Across all of the trials, when reported, overall catheter-related complications included pain in 50%, 42%, and 17% of patients [23,24,26], blockage in 9%, 26%, and 8% of patients [23,25,26], bleeding in 13% of patients [22], leakage in 18% and 4% [24,26] of patients, infection in 2%, 9% and 21% of patients [23,25,26], malfunction in 7% and 14% of patients [20,25], and peritonitis in 3%, 9%, and 2% of patients [20,23,24].

In one trial, the authors reported that catheters became dislodged in 11% of patients [24]. In the GOG 172 trial [26], although the differences were not statistically significant, catheter infections were more likely to occur in patients who required left colon surgery. The author's recommendation was to place IP catheters a few weeks after surgery if bowel resection was required. In that trial, reported in an additional paper, there was no relationship between appendectomy, small bowel resection or right colon resection and IP failure [27]. There were some difficulties in initiating the first cycle of IP therapy in patients who had left colon resection secondary to inability to place the infusion device. The recommendation from the study was that women could have IP catheters placed at the time of surgery provided contamination from bowel surgery did not take place. Additionally, catheters should be removed at the conclusion of treatment and not retained for future use, as the complication rates remain high.

## Quality of life

In the GOG 172 trial [26], the only trial to report quality of life outcomes, there were significantly lower quality of life scores detected for patients in the intraperitoneal chemotherapy arm prior to randomization, before the fourth cycle, and after the sixth cycle. Although the toxicities associated with IP chemotherapy were greater than that of IV chemotherapy, there were

**Table 4**  
Medical, surgical, and multidisciplinary criteria for the delivery of IP chemotherapy

**Rationale:** The management of patients with advanced ovarian cancer requires a multidisciplinary approach to ensure the best possible patient outcomes. Health care professionals should be suitably trained in the initial surgical management of patients with advanced disease, in the optimal timing, placement and type of catheter, and in the delivery of chemotherapy. Practitioners should also have advanced knowledge and experience with the complications associated with IP chemotherapy. Essential to the success of any intraperitoneal chemotherapy delivery program is the education and training of specialized nursing staff that are often the first line practitioners to encounter and recognize any potential problems with IP chemotherapy administration

#### Physician criteria

General characteristics for specialist involved in the management of patients with ovarian cancer receiving IP chemotherapy include:

- i. Advanced training and experience with the biology, behavior and natural history of ovarian cancer
- ii. Skilled in the modern techniques of gynecological cancer surgery including techniques required for the placement of intraperitoneal catheters to be used for the administration of IP chemotherapy
- iii. If involved, interventional radiologists need to be skilled in the placement of intraperitoneal catheters as required
- iv. Practitioners must be knowledgeable regarding the current treatment options for patients with advanced ovarian cancer
- v. Experience in the management of ovarian cancer patients, including the management of complications of this disease
- vi. Experience with the administration of treatments given for the management of ovarian cancer including the management of complications of treatment
- vii. Commitment in providing excellence in the care of ovarian cancer patients
- viii. Commitment in participating actively in a multidisciplinary care process
- ix. Commitment to ongoing quality analysis

#### Training criteria

- i. Surgeons should be trained in the insertion technique for placing intraperitoneal catheters for the administration of IP chemotherapy
- ii. Surgical gynecological oncologists should be skilled in the techniques of achieving maximum cytoreduction including gastrointestinal, gynecological and urological procedures
- iii. Surgical or medical oncologists should be knowledgeable about IP chemotherapy, its contraindications, toxicities and their management
- iv. Radiologists should have expertise in interventional insertion of catheters and their management

#### Nursing criteria

General characteristics for nurses involved in the management of patients with ovarian cancer receiving IP chemotherapy include:

- i. Knowledge of principles of administration of cytotoxic agents, more specifically of IP chemotherapy and of the agents used
- ii. Experience in administration and disposal of cytotoxic agents
- iii. Skilled in symptom assessment and management. Use of a validated assessment scale is recommended
- iv. Skilled in providing patient teaching
- v. Commitment in providing excellence in the care of ovarian cancer patients
- vi. Commitment in participating actively in a multidisciplinary care process, with a strong link with nurses in the community who provide care between treatments
- vii. Commitment to ongoing quality analysis

#### Training criteria

- i. Trained in administering IP chemotherapy (IP catheter care, patient assessment, administration, symptoms management, position change during the infusion)
- ii. Training of community nurses (visiting nurses) should be in place. This should include: principles of IP chemotherapy, patient assessment, symptoms management and catheter care

#### Clinical oncology pharmacist criteria

General characteristics for clinical oncology pharmacists include:

- i. Knowledgeable regarding current treatment options for patients with ovarian cancer
- ii. Specialized knowledge of cytotoxic chemotherapy administration (including via the IP route), including dosing, adverse effect prevention and management, and issues related to concomitant medication use
- iii. Experience in the provision of pharmaceutical care to ovarian cancer patients
- iv. Skilled in the provision of chemotherapy-related education to patients and caregivers
- v. Supported by a specialized chemotherapy preparation area
- vi. Commitment in providing excellence in the care of ovarian cancer patients
- vii. Commitment in participating actively in a multidisciplinary care process
- viii. Commitment to ongoing quality analysis and improvement

#### Training criteria

- i. Training in oncology pharmacy practice and clinical skills related to IP chemotherapy administration
- ii. Supported by pharmacy staff trained in the safe preparation of cytotoxic chemotherapy

no differences in quality of life scores at 1 year in that trial [26]. Interestingly, in a follow-up study, the authors report that patients with the poorest baseline quality of life scores were the least likely to complete IP chemotherapy [28].

## Discussion

As part of primary chemotherapy for patients with advanced ovarian cancer, three major randomized controlled trials have reported statistically significant improvements in median survival with cisplatin-based IP chemotherapy when compared with cisplatin-based IV chemotherapy [21,25,26]. Across the three trials, the survival benefits were observed even though the number of patients completing the planned cycles of IP chemotherapy ranged from 42% to 71% [21,25,26]. Most of the patients who discontinued treatment, either because of toxicity or patient choice, were able to continue with conventional IV chemotherapy, and regardless of the discon-

**Table 5**  
Practice setting of IP chemotherapy

**Rationale:** Since the delivery of IP chemotherapy is complex, a system-wide infrastructure that supports multidisciplinary teams of suitably trained professionals should be provided in a designated center able to meet the criteria outlined in Tables 4 and 6. Designated centers within regional gynecologic oncology programs or formal partnerships with regional programs are needed to work within the existing models of care

Practice setting requirements and volume of IP chemotherapy should include the following aspects:

- i. Intraperitoneal chemotherapy administration should be provided in a designated center within a regional gynecologic oncology program
- ii. Hospitals not meeting the requirements should establish formal relationships with such programs to ensure the optimal management of ovarian cancer patients including IP chemotherapy administration
- iii. Hospitals providing IP chemotherapy should treat a sufficient number of patients to ensure and maintain the skills needed for the provision of IP chemotherapy
- iv. Hospitals providing IP chemotherapy should have access to and participate in multidisciplinary tumor boards as part of a regional gynecologic oncology program

tinuation rates, the intention to treat analyses continued to demonstrate survival benefits. In theory, if tolerability can be improved and a higher proportion of patients receive all of the intended IP chemotherapy, there may even be a greater improvement in survival.

In terms of toxicity, the common feature of GOG 104, GOG 114 and GOG 172 trials is the use of IP cisplatin at doses of 100 mg/m<sup>2</sup> [21,25,26]. Cisplatin is significantly more emetogenic than carboplatin (the standard of care of platinum analogue when given intravenously). With cisplatin, longer duration of antiemetics and aggressive hydration are mandatory to enable patients to cope with chemotherapy-associated nausea, vomiting, and nephrotoxicity [29].

The catheter-related complications with IP chemotherapy were not reported consistently across the identified trials; however, complications did include abdominal pain, bleeding, infection, peritonitis, catheter blockage, leakage, movement, malfunction, and/or access problems. The standardization of care may help offset complications related to IP chemotherapy delivery. For example, Makhija et al. [30] reported a reduction in their complication rate from 17.6% to 10% by delaying insertion of the catheter, and many centers have now reduced the IP infusion volume from 2 to 1 l to decrease the discomfort related to abdominal distension. In addition, the use of implanted subcutaneous ports is now generally preferable to the use of Tenkoff peritoneal dialysis catheters, since Tenkoff catheters appear to cause erosion/infection, or fibrous sheath formations which may result in increased adhesions [31]. The evaluation of catheter type, insertion technique, and timing of insertion warrants further investigation in upcoming studies.

There is much debate in the literature both for [12–18] and against [32–35] the use of IP chemotherapy as part of current clinical practice. Gore et al. [32] stated several concerns with the use of IP chemotherapy, and particularly with the findings of GOG 172 trial [26]. The authors questioned whether the small statistically significant benefits detected in the Armstrong trial ( $p=0.03$ ) may have been offset had the study conducted intention to treat analyses (14 patients were excluded from the analysis), and they questioned whether the absolute benefit of IP chemotherapy warranted the increase in toxicity and reductions in quality of life. There were also concerns that the cisplatin-based experimental arms were not compared to control arms with carboplatin and paclitaxel, and that there was no clearly defined IP chemotherapy regimen that could be considered safe enough to offer patients, with level 1 evidence of efficacy, outside the context of a randomized controlled trial [32]. In addition, the conclusions from the Third International Consensus Conference on Ovarian Cancer in 2004 were that IP chemotherapy “remains controversial, and therefore its use has not been widely adopted” [33,34].

In a 2006 rebuttal by Armstrong and Brady [36], the authors note that the statistically significant improvement in survival was more pronounced when excluded patients were added to the analysis. They commented that the toxicities could be better managed through more experience and the appropriate expertise in the treatment center, that quality of life was similar between treatment groups at 12 months, the absolute difference in

survival was a poor measure since treatment only delays death, not prevents it, and most importantly, that IP chemotherapy was responsible for improvements in survival in their trial and in other trials as well. The authors concluded that the lack of consensus on the optimum treatment regimen should not discourage clinicians from offering IP chemotherapy in the clinical setting [36]. The findings from a 2006 GOG workshop on IP chemotherapy were supportive of the use of IP chemotherapy, and in addition to practical implementation issues provided; the primary conclusion was that informed

Table 6

Institutional criteria for the delivery of IP chemotherapy

Rationale: There are important institutional characteristics to consider if IP chemotherapy is to be offered to patients on a routine basis. Specific hospital criteria, physical resources and collaborating services, human resources, and organizational criteria need to be considered if the optimal care of patients is to be achieved with this chemotherapeutic delivery system

*Hospital criteria*

- i. Commitment to high-quality best practice care for ovarian cancer patients
- ii. Commitment in providing the resources required to ensure the safe and efficacious provision of IP chemotherapy to ovarian cancer patients
- iii. Commitment to ongoing quality assurance evaluation

*Physical resources and collaborating services*

The following physical resources and collaboration services are necessary in the provision of IP chemotherapy for ovarian cancer:

- i. A safe environment in which the patient will receive IP chemotherapy
- ii. An on-site rapid response laboratory for biochemistry, hematology, transfusion assessment, microbiology
- iii. A pharmacy preparation area that meets all the requirements for modern chemotherapy preparation and safety
- iv. Access to the operating room and treatment facilities to manage complications of therapy including removal and placement of catheters and abdominal surgery
- v. Affiliation to a regional cancer care program/center
- vi. Established multidisciplinary tumor boards or a formal relationship with such for patient review and assessment
- vii. Established policies and procedures for managing toxicity and delivery
- viii. Specialized training programs/rounds/continuing education for nurses in the delivery of IP chemotherapy
- ix. Ward access for complications and admissions of patients
- x. A formalized outpatient follow-up care process

*Human resources*

Human resources should include:

- i. Gynecologic oncologists
- ii. Medical oncologists (or gynecologic oncologists skilled in chemotherapy delivery)
- iii. Skilled and trained nursing staff (both within gynecologic oncology programs and in the community)
- iv. Skilled and trained pharmacy staff
- v. Allied professionals skilled in the care of ovarian cancer patients
- vi. Access to other consulting specialists as required (i.e., infectious diseases, vascular, etc.)
- vii. Access to interventional radiologists with expertise in IP catheter insertion and management and radiological services (abdominal X-rays, CT scan, MRI)

*Organizational criteria*

- i. A multidisciplinary team approach (formalized, documented case based)
- ii. A designated gynecologic oncology unit with identified leadership and accountability or a formal relationship with such
- iii. A system for regular review in IP chemotherapy administration (i.e., quality assurance, outcome measurement, dissemination of outcome indicators, ongoing educational initiatives, morbidity and mortality review)
- iv. Collaboration in networks of care to maintain, standardize and improve the provision of IP chemotherapy

patients should ultimately make the choice of whether or not to receive IP chemotherapy [37].

As the role of IP chemotherapy continues to evolve, it is clear that the observed survival benefits are offset by toxicities and challenges associated with a delivery route that is not commonly employed in current Canadian clinical practice, but is one that is gaining acceptance. In a recent Canadian survey which captured the opinions of 62% of Canadian Gynecologic Oncologists, 81% of respondents reported that they were actively working toward implementing IP chemotherapy at their cancer centers [38]. If IP chemotherapy is to be considered now, or in the future when further data become available, standards of care with the appropriate treatment setting and team infrastructure need to be established.

Standards of care and management recommendations for IP chemotherapy delivery in Canada were developed through a series of consensus meetings involving a multidisciplinary expert panel on the treatment of ovarian cancer (Tables 3–6). The standards emphasize that care is optimally provided within the setting of a multidisciplinary care process, a setting known to improve patient outcomes. Also, critical to the treatment of advanced disease is the involvement of gynecologic oncologists, as there is evidence to support that superior outcomes are achieved when gynecologic oncologists are involved in the surgical care of patients with ovarian cancer [2–4]. The expert panel identified gaps in practice relating to the provision of IP chemotherapy within the context of the Canadian cancer care system with several considerations in mind. If IP chemotherapy were to be successfully offered as part of routine therapy, then standards concerning medical and surgical criteria, practice settings, caseloads of IP chemotherapy, and institutional criteria, would be needed as an integral part of a system-wide model. As well, a quality assurance component would be critical to monitor outcomes and proficiency over time and as the treatment modality does evolve, a built-in knowledge exchange component would also be needed to disseminate information in a timely manner.

The purpose of standards of practice for IP chemotherapy is not only to inform about current practice requirements, but to also acknowledge that IP chemotherapy might have wider application as more data become available. Not only does this require built-in flexibility within the current cancer care system, but it affords a rare opportunity to create a community of practice. Because of the timeliness and uniqueness of the issues surrounding the delivery of IP chemotherapy, the cooperative effort of many clinicians, all working toward a specific standard, will result in a ‘raising of the bar’ to optimize therapies for patients with ovarian cancer.

## Conclusion

Level I evidence suggests a significant survival benefit for cisplatin-based IP chemotherapy in women with optimally debulked stage III epithelial ovarian cancer. There is however an increase in short-term toxicity for the combined IP/IV regimen when compared with IV chemotherapy alone. Toxicity relates to the regimen employed, the mode of administration, and the presence of the abdominal catheter. Toxicity can be

minimized by being aware of the potential side effects and by adopting a proactive policy to ensure they are kept to a minimum and are dealt with rapidly.

There is a disconnection between the increasing interest of IP chemotherapy as part of primary treatment in optimally debulked patients with stage III ovarian cancer, and the current capacity to deliver the treatment safely. If IP chemotherapy is to be routinely offered to patients, system-wide guidance on the practical application of the delivery of care is warranted. It is hoped that the standards presented will help set the necessary requirements for the medical and surgical criteria, the practice setting, institutional criteria, and number of IP chemotherapy administrations, needed to successfully deliver IP chemotherapy currently and in the future. Additional educational and practical materials are available from the American Gynecologic Oncology Group website ([www.gog.org](http://www.gog.org)).

The GOC endorses the use of IP chemotherapy, the baseline protocol being the GOG 172 regimen, for patients with optimally debulked advanced ovarian cancer. To address toxicity, further adjustments to the protocol should be made within the context of the appropriate multidisciplinary clinical and institutional facilities. There is the debate and potential concern that significant variations from the GOG 172 regimen may mitigate some of the survival benefits detected. Future efforts should be directed at improving patient outcomes over and above what is achievable with the cisplatin-based IP regimen currently recommended. Awaiting the development of targeted therapies, carboplatin-based regimens investigated in the randomized setting, together with the ongoing refinement of techniques and devices may hold promise for this patient population as IP chemotherapy gains acceptance in clinical practice.

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## Appendix A (continued)

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