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Original Article

Toxicity of intraperitoneal chemotherapy and risk factors for severe toxicity in optimally debulked ovarian cancer patients

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ABSTRACT

Objective: To assess the effect and toxicity of intraperitoneal (IP) chemotherapy for epithelial ovarian cancer and to determine the risk factors for severe toxicity.
Materials and methods: Patients who received IP chemotherapy after optimal debulking surgery for ovarian cancer between 2006 and 2012 were retrospectively reviewed. Clinical characteristics were compared between patients with none/Grade 1 or Grade 2 toxicity and those with Grade 3 or Grade 4 toxicity.
Results: In 41 patients, the mean number of IP cycles administered was 5.6 and most patients (80.5%) completed at least six cycles. The reasons for discontinuation were catheter-related problems (30%), disease progression (20%), or drug-related adverse effects (30%). Grade 3 or Grade 4 toxicity was observed in 30 patients (73.2%). The rate of neoadjuvant chemotherapy was higher in the patients with Grade 3 or Grade 4 toxicity (37%) than in the patients without Grade 3 or Grade 4 toxicity (9%), however, this difference was not significant ($p = 0.128$). During a mean follow-up period of 33.6 months, tumor recurrence occurred in 20 (48.8%) patients and the median progression-free survival was 30.0 months.
Conclusion: Despite the high rate of adverse events, IP chemotherapy can be delivered with a high completion rate and manageable toxicity to patients with optimally debulked ovarian cancer. Toxicity should be closely monitored in patients who have received neoadjuvant chemotherapy until a large prospective study can be performed to determine its influence.
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Introduction

Among gynecologic malignancies, ovarian cancer is the leading cause of death worldwide, with 224,747 new cases and 140,163 deaths attributed to this disease in 2008 [1]. In the United States, ovarian cancer was the second most prevalent malignancy of the female genital system and the number one cause of gynecological cancer deaths in 2012.

The amount of residual tumor remaining after surgery is a major prognostic factor in ovarian cancer; furthermore, tumors tend to be chemosensitive. The standard treatment for epithelial ovarian cancer (EOC) therefore involves cytoreductive surgery followed by intravenous (IV) chemotherapy with a platinum-based agent with or without taxane. Nevertheless, recurrence is common; 70% of patients develop peritoneal disease and the median overall 5-year survival rate of patients with EOC is <50%.

EOC is most likely to present as a tumor that has metastasized throughout the peritoneal cavity. Based on this rationale, there is increased attention on intraperitoneal (IP) chemotherapy, which refers to direct infusion of the chemotherapeutic regimen into the peritoneal cavity. As one of several randomized controlled trials, the Gynecologic Oncology Group (GOG) 172 performed a milestone study of survival outcomes. A significant improvement in both progression-free survival (PFS) and overall survival (OS) was observed in the IP arm; the median PFS was 18.3 months for the IV arm and 23.8 months for the IP arm, whereas the median OS was 49.7 months for the IV arm and 65.6 months for the IP arm [2].

Nevertheless, the standard frontline management has, for the most part, not changed, and IP chemotherapy is still not routinely offered in current clinical practice. The main reasons for this are concerns about toxicity and catheter-related complications,

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followed by not having the facilities to provide IP infusions [3]. Because of these limitations, IP chemotherapy is not widely used even in tertiary referral centers in Korea, and only a few studies regarding intraoperative single administration of cisplatin alone or IP administration of these agents as a consolidation treatment after secondary surgery have been reported [4,5]. In this study, we assessed the effect and toxicity of IP chemotherapy for EOC and determined the risk factors for severe toxicity during IP therapy.

Materials and methods

We retrospectively collected data from patients who had received IP chemotherapy following cytoreductive surgery for EOC between November 2006 and September 2012. The analysis was restricted to newly diagnosed disease, of any stage according to the International Federation of Gynecology and Obstetrics (FIGO), following cytoreductive surgery with residual tumor measuring $\leq$1 cm.

Neoadjuvant chemotherapy was performed in some patients based on their clinician's preference, and a combination agent consisting of carboplatin (area under the curve, 5) and IV paclitaxel (175 mg/m^2) was used for three to six cycles every 21 days. After surgical debulking, all patients were treated with six cycles of IP chemotherapy every 21 days using a protocol similar to that used in the GOG 172 study: IV paclitaxel (135 mg/m^2) over 24 hours on Day 1 followed by IP cisplatin (100 mg/m^2) on Day 2 and IP paclitaxel (60 mg/m^2) on Day 8. A BardPort M.R.I. implanted port (Bard Access Systems, Inc., Salt Lake City, UT, USA) with a 9.6-Fr open-ended single lumen catheter was used for this purpose. Before chemotherapeutic agents were administered, standard premedications, including antiemetic and antihypersensitive drugs, were given, and 500 mL of warmed normal saline was infused before and after IP cisplatin administration for hydration.

A retrospective chart review was carried out. Demographic characteristics, pathology reports, and progressive courses related to chemotherapy-related complications and disease progression were obtained from medical records. All toxicities were graded according to the Common Toxicity Criteria for Adverse Events version 4.0. Patients with greater than Grade 1 neutropenia were treated with granulocyte colony-stimulating factor (G-CSF) to achieve an absolute neutrophil count of $\geq 1.5 \times 10^9$/L. Although our institution has no strict guidelines, IP chemotherapy was discontinued and switched to an IV protocol when initial modifications, such as dose reduction and cycle delays for up to 2 weeks, failed to improve drug-related toxicity. Completion was defined by receipt of all courses planned before starting IP chemotherapy infusion. Any Grade 3 or Grade 4 toxicity was considered to be severe toxicity, and clinical characteristics were compared between patients with or without severe toxicity during IP therapy.

During chemotherapy, the serum cancer antigen 125 (CA 125) level was routinely measured before every cycle of chemotherapy, and positron emission tomography/computerized tomography (PET/CT) imaging was used for every three cycles of chemotherapy to estimate disease progression. After completing the initial treatment, routine follow up comprising a clinical examination and CA125 level check were performed every 3 months for the next 2 years and every 3–6 months for the following 3 years. A PET/CT scan was performed every 6–12 months for 5 years or when clinically indicated. PFS was determined from the date of primary surgery to the date of first recurrence or the date of last follow up. OS was determined from the date of primary surgery to the date of death or the date of last follow up.

Continuous variables were compared using a paired t test, and categorical variables were compared with a two-tailed Chi-square test. SPSS version 12 (SPSS for Windows, Release 12; SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. A p value < 0.05 was taken to be significant.

Results

All 50 EOC patients were treated with IP chemotherapy at Cheil General Hospital and Women's Healthcare Center, Seoul, Korea between November 2006 and March 2012. Nine patients who had a residual tumor larger than 1 cm after surgery and those who had received IP chemotherapy for a recurrent tumor were excluded from analysis.

The mean age of the 41 patients at presentation was 49.1 years and the mean body mass index (BMI) was 22.7 kg/m^2 (Table 1). Thirteen (31.7%) patients had undergone at least one previous abdominal surgery. In all cases, cytoreductive surgery was performed via the abdominal route, and the catheter for chemotherapy was placed intraperitoneally at the time of the initial debulking surgery. Most patients had FIGO Stage IIIC tumors (n = 23, 56.1%), followed by FIGO Stage IC (n = 9, 22%). With respect to histology, serous type was most common (n = 25, 61%) followed by mucinous-type tumors (n = 5, 12.2%).

Neoadjuvant chemotherapy with IV paclitaxel and IV carboplatin was performed in 12 (29.3%) patients as follows: three cycles in seven patients, four cycles in one patient, and six cycles in four patients (Table 2). The mean time to start of IP chemotherapy after surgery was 13.2 days and the mean number of IP chemotherapy cycles administered was 5.6. Thirty one (75.6%) of the 41 patients completed all the prescribed IP cycles. Discontinuation was required in 10 (24.4%) cases, two of which had been scheduled to have all nine cycles of IP chemotherapy, including three cycles of consolidation therapy. Thus, 80.5% (n = 33) of patients successfully received IP chemotherapy for at least six cycles, and 85.4% (n = 35) of patients successfully received IP chemotherapy for at least five cycles. However, a delay in chemotherapy duration of >3 days was

Table 1
Demographic characteristics and surgical findings of 41 patients who received IP chemotherapy following cytoreductive surgery for epithelial ovarian cancer.

Variable	
Age (y)	49.1 ± 10.3
Parity	1.9 ± 1.0
BMI (kg/m^2)	22.7 ± 3.0
Previous abdominal surgery	13 (31.7)
CA125 (U/mL)	783.8 ± 1662.0
Initial tumor size (cm)	9.1 ± 5.5
FIGO stage	
IC	9 (22.0)
IIC	3 (7.3)
IIIA	3 (7.3)
IIIB	3 (7.3)
IIIC	23 (56.1)
Residual mass size	
Grossly none	35 (85.4)
≤1 cm	6 (14.6)
Histology	
Serous	25 (61.0)
Mucinous	5 (12.2)
Endometrioid	1 (2.4)
Clear cell	7 (17.1)
Others	3 (7.3)
Grade	
1	5 (12.2)
2	6 (14.6)
3	26 (63.4)
Undetermined	4 (9.8)
Second-look surgery after IP chemotherapy	21 (51.2)

Data are presented as n (%) or mean ± standard deviation.
BMI = body mass index; FIGO = International Federation of Gynecology and Obstetrics; IP = intraperitoneal.

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