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The Effectiveness of Intraperitoneal Carboplatin-Taxane Combination Chemotherapy in Stage 3 Ovarian Cancer

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ABSTRACT

Objective: Our purpose is comparing the effectiveness of IP and IV chemotherapy in patients with epithelial ovarian cancer (EOC). This is a pilot study for improving protocol of chemotherapy for EOC.

Methods: A retrospective, single-center study included 103 patients with EOC between March 2005 and December 2022. Forty-eight patients received IV chemotherapy; 45 received IP chemotherapy. In the IP group, carboplatin (AUC5) was administered on day 1 and paclitaxel (135 mg/m^2) was on day 2 through IP port, every three weeks for 6 cycles. In the IV group carboplatin and paclitaxel were administered intravenously with the same dosage and the same schedule. The primary endpoint was progression free survival.

Results: The median PFS was longer in the IP group than in the IV group (65 months vs. 59 months) with 31% lower risk of recurrence (HR=0.69, 95% CI: 0.35-1.34, P=0.27). The median PFS of stage 3 was 47 months (95% CI: 15.8-78.1) with the IP chemotherapy and 19 months (95% CI: 16.22-21.77) with IV chemotherapy (HR=0.36, 95% CI: 0.14-0.95, P=0.04). Median OS for patients of stage 3 was 110 months and 67 months in the IP group and IV group (P=0.03), respectively (HR=0.17, 95%CI: 0.03-1.08, P=0.06).

Conclusion: IP chemotherapy has a survival benefit in patients with stage 3 EOC. There were no significant differences in adverse events between two groups.

KEYWORDS: Ovary cancer, Intraperitoneal chemotherapy, Carboplatin-taxane

INTRODUCTION

Ovarian cancer is the most lethal gynecological malignancy, because diagnosing ovarian cancer at an early stage is difficult due to the absence of specific symptoms. The standard treatment for ovarian cancer is primary debulking surgery[1] followed by adjuvant platinum- and taxane-based combination chemotherapy.[2,3] Ovarian cancer shows good responses to primary therapy but has high recurrence and mortality rates.

Recently, poly-adenosine ribose polymerase (PARP) inhibitors, immune checkpoint inhibitors and targeting agents such as olaparib, niraparib, pembrolizumab, and bevacizumab have been for maintenance therapy and improved treatment outcomes.[4,5] Additionally, a drug for platinum-resistant ovarian cancer, mirvetuximab soravtansine, an antibody-drug conjugate (ADCs), has offered a survival benefit to patients with high folate receptor alpha.[6] Even though successful targeting therapies, platinum- and taxane-based combination chemotherapy remains the standard treatment for ovarian cancer. Therefore, efforts to improve the efficacy of traditional chemotherapies should be continued.

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Intraperitoneal (IP) chemotherapy, dose dense chemotherapy, hyperthermic intraperitoneal chemotherapy (HIPEC) have been known to increase survival compared to conventional intravenous (IV) chemotherapy in epithelial ovarian cancer (EOC) patients.[7-10]

In GOG-172, Intraperitoneal Therapy for Ovarian Cancer with Carboplatin (iPocc) trial, and GOG-252, the chemotherapy delivery route (IV versus IP) was not the only factor affected on survivals because the dosage and schedule of the drugs were different.[7, 11, 12] And the combination of IP chemotherapy with platinum and taxane has not yet been reported. This study aimed to compare IP and IV chemotherapy at the equivalent dosage and schedule. Therefore, we retrospectively evaluated the outcomes of combination IP chemotherapy.

METHODS

1. Study design and patients

In this retrospective, single-center study, we reviewed medical record of patients with EOC who received carboplatin-taxane chemotherapy at the Hallym University Sacred Heart Hospital between March 2005 and December 2022. The inclusion criteria were as follows: (1) patients diagnosed with EOC, tubal cancer, or primary peritoneal cancer; (2) patients who had received neoadjuvant chemotherapy or adjuvant chemotherapy with debulking surgery; (3) patients who had received at least three cycles of carboplatin-taxane chemotherapy; and (4) a follow-up period of at least six months after the first chemotherapy.

The exclusion criteria were as follows: (1) patients with nonepithelial ovarian cancer or borderline malignancy; (2) patients under treatment for another malignancy; (3) patients with an European Cooperative Oncology Group (ECOG) status of 3 or 4; (4) patients who experienced recurrence within less than 6 months; (5) patients under the age of 19 years, and (6) pregnant women.

Among 118 patients, fifteen patients were excluded based on the exclusion criteria. Four patients died or were referred to other center after surgery; two refused chemotherapy; six received chemotherapy for less than three cycles; one received chemotherapy at our center for only one cycle; and two were not diagnosed with EOC. Finally, 103 patients were included; 48 were in the IV chemotherapy group and 45 were in the IP chemotherapy group. There were 8 patients received IP chemotherapy after recurrence in IV chemotherapy group. Patients with platinum-resistant EOC that had progressed or recurred within six months of chemotherapy were excluded (six patients in the IV group and four patients in the IP group) (Fig. 1).

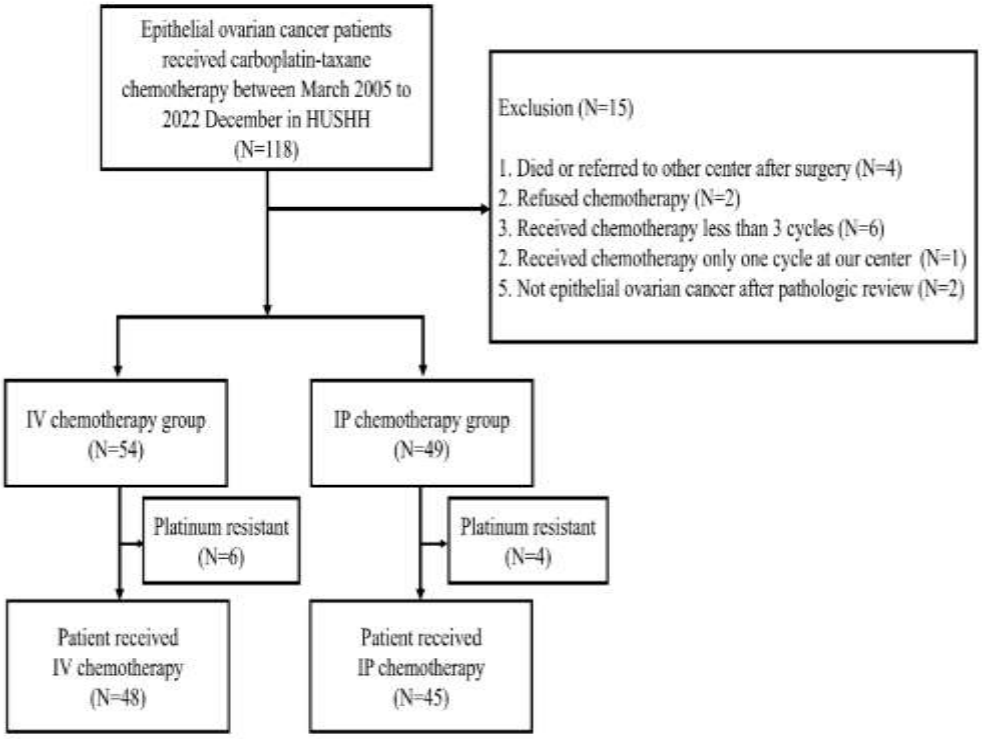

Figure 1. Flow diagram of this study.

IV, Intravenous; IP, Intraperitoneal

2. Outcome

The primary outcome of this study was progression free survival (PFS). PFS was defined as the interval between the date of the first chemotherapy cycle and the time of disease progression or death. The secondary outcomes of this study were overall survival (OS) and severe adverse events (Common Terminology Criteria for Adverse Events version 5.0, grades 3-5) of chemotherapy. OS was defined as the interval between the date of surgery or the first cycle of chemotherapy and death. Disease progression was evaluated

according to the Response Criteria in Solid Tumors criteria and serum CA125 levels. Recurrence was diagnosed based on biopsy findings, elevated CA125 levels, or radiological findings.

3. Treatment

Patients were pathologically diagnosed with ovarian cancer using debulking surgery or biopsy. Patients underwent primary debulking surgery with adjuvant chemotherapy or neoadjuvant chemotherapy with debulking surgery. Imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI), were performed after the end of chemotherapy. After recurrence, patients received chemotherapy with or without secondary cytoreductive surgery.

The regimen of chemotherapy was carboplatin (area under the curve (AUC) 5) on day 1 and paclitaxel (135 mg/m^2) on day 2, every three weeks in both groups (Fig. 2). Carboplatin was administered for 4 h and paclitaxel for 24 h, in the IV group. In the IP group, carboplatin was infused into the intraperitoneal space for > 4 h on day 1 and paclitaxel for 1h on day 2. Chemotherapy was administered at least 6 cycles, and 3 to 6 more cycles were added if there was residual disease on follow-up studies. Ultrasonography was performed before chemotherapy, to assess the function of the IP port in the IP group.

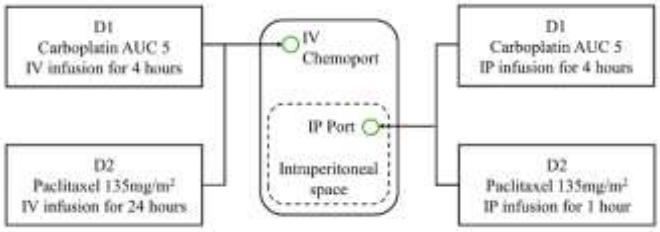

Figure 2. Drug administration of IV and IP group.

IV, Intravenous; IP, Intraperitoneal; AUC, Area under curve

4. Follow-up

After treatment, patients were followed -up every three months in the first two years and every six months from the third year. During the follow-up period, serum CA125 levels were measured, imaging studies such as CT, MRI, or ultrasonography were performed, and other symptoms were recorded.

5. Statistical Analysis

The data were analysed using IBM Statistical Package for the Social Sciences (SPSS) version 28. PFS and OS were calculated using Kaplan-Meier curves and Log-rank test. Eight patients underwent IP chemotherapy after recurrence (IP group in Fig. 2). They were excluded when calculating OS as this study were aimed to compare IP chemotherapy as first-line regimen. Otherwise, patients received IP chemotherapy at least three cycles are classified to IP chemotherapy. Chi-square and Fisher's exact tests were used to analyse the recurrence rates of the two groups. Baseline characteristics of two groups were assessed using Chi-square test. Cox's proportional hazard model was used to assess Hazard ratios (HR) of chemotherapy route, histologic type and grade. Statistical significance was set at a p value < 0.05. We used Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist to for reporting this retrospective study.

6. Ethics statement

This study was conducted according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Hallym University Sacred Heart Hospital (IRB No. HALLYM 2023-04-010-00

RESULTS

Baseline characteristics are described in Table 1. There were no significant statistical differences between two groups for age at diagnosis, menopausal state, weight, BMI, and residual tumor size after surgery. There were some patients that information of grade was not available in their pathologic reports; 21 in the IV group, and 11 in the IP group. It is difficult to review pathologic slides because it is retrospective study.

Table 1. Baseline characteristics.

	IV group (N=48)	**IP group (N=45)**	**p-value**
Age(y), mean±SD	57.5±13.9	53.4±11.3	0.38
Menopausal state			0.24
Premenopause	14	21	
Menopaused	25	22	

Unknown	9	2	
Weight(kg), mean±SD	60.9±8.9	59.3±9.1	1.00
BMI(kg/m^2), mean±SD	24.8±3.3	24.2±3.2	0.70
Residual tumor after surgery			0.26
Microscopic	24	23	
0<diameter≤1cm	6	11	
>1cm	17	11	
N/A	1	0	
Histologic type			0.053
Serous	30	28	
Mucinous	5	3	
Endometrioid	1	9	
Clear cell	10	4	
Transitional	1	0	
Undifferentiated	1	1	
Histologic grade			0.63
Low	7	13	
Moderate-high	17	24	
N/A	24	8	
FIGO stage			
1	17	8	
2	3	6	
3	13	26	
4	15	5	

BMI, Body Mass Index; N/A, Not available

In the IV group, four patients were lost to follow- up and two patients were under ongoing chemotherapy. In the IP group, two patients were lost to follow- up and four patients were under ongoing chemotherapy. The follow-up duration ranged from 6 to 175 months. The median follow-up duration was 35 months.

The median PFS was longer in the IP group than in the IV group (65 months vs. 59 months, P=0.27) with 31% lower risk of recurrence in the IP group than in the IV group (HR=0.69; 95% confidence interval [CI]: 0.35-1.34, P=0.27). The median PFS of stage 3 was 47 months (95% CI: 15.8-78.1) with the IP chemotherapy and 19 months (95% CI: 16.22-21.77) with IV chemotherapy (HR=0.36, 95% CI: 0.14-0.95, P=0.04) (Fig. 3). The median PFS in stage 4 was 18 months (95% CI: 6.79-29.2) in the IP group and 23 months (95% CI: 9.74-36.25) in the IV group (HR=2.21, 95% CI: 0.52-9.34, P=0.25). The median PFS for stage 1 and 2 was not determined.

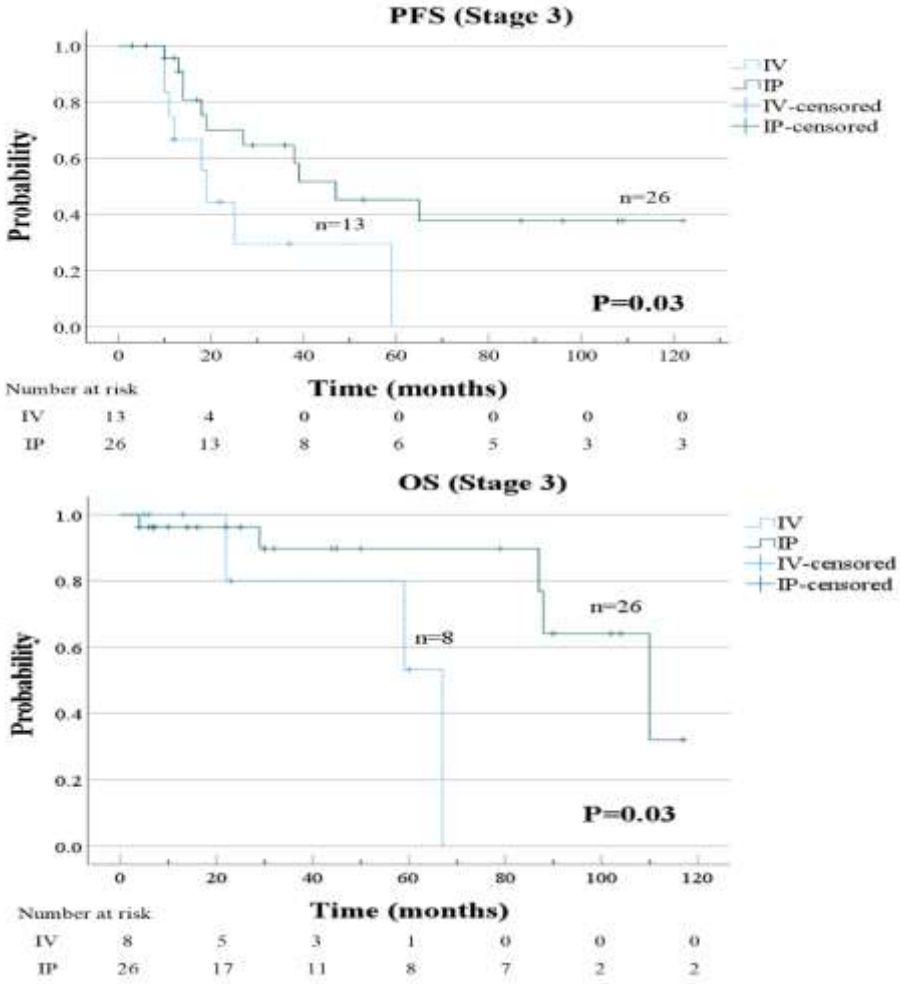

Figure 3. Progression-free survival and overall survival of IV and IP group.

The median OS of patients with stage 3 was 110 months and 67 months in the IP group and IV group (P=0.03), respectively (HR=0.17, 95% CI: 0.03-1.08, P=0.06). The median OS was not determined in the early stages (stage 1 and 2) or stage 4.

The clear cell carcinomas were included in both groups; 10 patients in IV group (8 in stage 1, and 2 in stage 4), and 4 patients in IP group (1 in stage 1, 2 in stage 2, and 1 in stage 3). There was no patient with clear cell carcinoma included in the IV group with stage 3 ovarian cancer and one patient included in the IP group.

The number of patients with recurrence was 37 (39.8%) in total; 22(45.8%) in the IV group and 15 (33.3%) in the IP group (P=0.30). The recurrence rates of stage 3 disease were 69.2% (9 of 13 patients) and 42.3% (11 of 26 patients) in the IV and IP groups, respectively (P=0.21). The recurrence rate of stage 4 disease was 46.67% (7 of 15 patients) in the IV group and 60.0% (3 of 5 patients) in the IP group (P=0.50).

Hematological adverse events were the most common (Table 2). 39 patients (86.7%) in the IP group and 44 patients (91.7%) in the IV group reported leukopenia (P=0.44). Anemia was present in 19 (42.2%) and 24 patients (50.0%) in the IP and IV groups, respectively (P=0.45). Adverse events were not statistically significant.

Table 2 Severe adverse events (CTCAE version 5.0, Grade 3~5)

	IV group (N=48)	**IP group (N=45)**	**p-value**
Anemia	24 (50.0%)	19 (42.2%)	0.45
Leukopenia	44 (91.7%)	39 (86.7%)	0.44
Thrombocytopenia (Platelet count <50,000/mm3)	21 (43.8%)	15 (33.3%)	0.30
Liver enzyme elevation	5 (10.4%)	6 (13.3%)	0.66
Hypokalemia	14 (29.2%)	18 (40.0%)	0.27
Hyponatremia	4 (8.3%)	9 (20.0%)	0.11

Renal failure	3 (6.3%)	4 (8.9%)	0.63
Heart failure	1 (2.1%)	0 (0.0%)	0.33
Sepsis	4 (8.3%)	3 (6.7%))	0.76
General weakness	1 (2.1%)	1 (2.2%))	0.96
Anaphylaxis	1 (2.1%)	0 (0.0%)	0.33
Neuropathy	1 (2.1%)	1 (2.2%)	0.96
MI	0 (0.0%)	1 (2.2%)	0.30
PTE	0 (0.0%)	1 (2.2%)	0.30

IV, Intravenous; IP, Intraperitoneal; MI, Myocardial infarction; PTE, Pulmonary thromboembolism; CTCAE, Common Terminology Criteria for Adverse Events

DISCUSSION

The results of this study found that IP chemotherapy appears to have survival benefit in stage 3 platinum sensitive EOC patients. PFS gain was 28 months and median OS gain was 43 months in the IP group. However, IP chemotherapy might be not effective for stage 4 ovarian cancer as PFS of the IP group was shortened by 5 months. Adverse events were not different from each other.

Ovarian cancer spreads within the peritoneal cavity rather than hematogenous or lymphatic route. DeGregorio et al. and Markman et al. reported peritoneal/plasma ratio of peak concentrations of drugs is high in IP chemotherapy; peak peritoneal concentration of carboplatin is 24-fold higher than plasma level and AUC of paclitaxel is 1000-fold higher in the peritoneal curve than the plasma curve.[13-15] Therefore, IP chemotherapy directly exposes chemotherapeutic agents to intraperitoneal tumors in high concentration.

In this study, patients received paclitaxel with 135 mg/m^2 rather than 175 mg/m^2. In GOG-158, carboplatin AUC 7.5 with paclitaxel 175 mg/m^2 was administered to optimally debulked ovarian cancer patients, median PFS and median OS of stage 3 were 19.4 months and 48.7 months.[16] Although patients with residual tumor size >1cm after surgery and used lower dose of carboplatin than that of GOG-158 in this study, survival months of the IV groups were similar in both studies.

There have been three recent trials on IP chemotherapy; GOG-172, iPocc trial, and GOG-252. GOG-172 compared IV and IP chemotherapy using cisplatin and taxane in stage 3 ovarian cancer, median PFS was 18.3 months and 23.8 months in the IV and IP groups, respectively (P=0.05).[7] The iPocc trial included patients with stage 2-4 ovarian cancer who were administered carboplatin IV vs. IP with IV taxane.[11] They exhibited improved median PFS, 20.7 months in the IV group and 23.5 months in the IP group (P=0.04). GOG-252 compared IV and IP chemotherapy when administered IV taxane (weekly 80 mg/m^2) and bevacizumab (15 mg/kg).[12] Median PFS was 24.9 months, 27.4 months, and 26.2 months in IV carboplatin, IP carboplatin, and IP cisplatin, respectively.

Recently, a clinical trial conducted by Lim et al. compared IV and HIPEC with cisplatin.[17] The median PFS of stage 3 and 4 ovarian patients was 18.8 months in the HIPEC group and 19.8 months in the control group. In our study, the median PFS was 19 months in the IV group and 39 months in the IP group in patients with stage 3 and 4 ovarian cancer. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin is a new model suggested in platinum resistant or recurrent ovarian cancer.[18]

This study had several strengths. First, the same dosage and schedule of chemotherapy were administered to both groups. This study is the first to compare the IV and IP routes of carboplatin taxane administration in patients with ovarian cancer. Second, although the taxane dosage used in this study (135 mg/m^2) was the dosage of taxane used in GOG 172 and it is lower dosage used in the other studies,[7] the survival rate was better in the IP group, and adverse events were not different between the two groups. Third, according to GOG 252, IP chemotherapy is not superior to IV chemotherapy when bevacizumab is administered: however, GOG 252 included patients with stage 2-4 ovarian cancer. In our study, subgroup analysis revealed a survival benefit of IP chemotherapy in patients with stage 3 ovarian cancer.

This study had several limitations. First, the catheter- related complications, such as infection, leakage, and wound dehiscence were not evaluated. Second, peritoneal adhesions can be a barrier to continue IP chemotherapy. When the infusion rate was delayed, route of chemotherapy was changed to IV catheter in the IP group. Third, this was a retrospective, single-center study with a small sample size, so there could be selection bias and a lack of generalizability.

In the future, prospective randomized controlled trials limited to stage 3 and an investigation of the differences between the stages are necessary. A combination of IP carboplatin- taxane chemotherapy with maintenance therapy such as immune checkpoint inhibitors, PARP inhibitors and bevacizumab, may be necessary.

In conclusion, IP chemotherapy is a better choice than IV chemotherapy in stage 3 EOC. However, IV chemotherapy could be a better choice than IP chemotherapy for patients with stage 4 ovarian cancer.

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Conflict of interest
All authors have no conflicts of interest to declare.

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