Are Three Additional Cycles of Chemotherapy Useful in Patients with Advanced-stage Epithelial Ovarian Cancer After a Complete Response to Six Cycles of Intravenous Adjuvant Paclitaxel and Carboplatin?†

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Background: To evaluate the efficacy of three additional cycles of chemotherapy in patients with the International Federation of Gynecology and Obstetrics Stage III or IV, who achieved a complete response after six cycles of intravenous adjuvant paclitaxel/carboplatin after surgery.

Methods: The clinical data of 94 patients with complete response after six cycles of adjuvant paclitaxel/carboplatin after surgery between January 1997 and March 2007 were reviewed retrospectively. Three additional cycles using the same chemotherapy were administered to 57 patients as consolidation chemotherapy (Group 1). Thirty-seven patients without the additional cycles served as controls (Group 2). Disease-free survival (DFS) and overall survival (OS) were evaluated using the Kaplan−Meier method with the log-rank test. The importance of consolidation chemotherapy as a prognostic factor affecting survival was examined using the Cox's proportional hazard analysis. The incidence of chemotherapy-induced hematological toxicities was compared between the two groups using chi-square test.

Results: Median DFS and mean OS were not significantly different between the two groups (15 versus 22 months, $P = 0.703$; 69 versus 73 months, $P = 0.891$, respectively). Consolidation chemotherapy was not a prognostic factor of survival although optimal debulking surgery and lower value of serum CA-125 levels after six cycles of the chemotherapy were prognostic factors improving DFS ($P < 0.01$). Grade 3 or 4 leukopenia was more common in patients treated with consolidation chemotherapy than in those not treated (50.9 versus 21.6%, $P = 0.004$).

Conclusion: Consolidation chemotherapy using paclitaxel/carboplatin may be inefficient and relatively toxic to advanced-stage epithelial ovarian cancer patients with complete response to six cycles of the same chemotherapy after surgery.

Key words: consolidation chemotherapy − paclitaxel − carboplatin − ovarian cancer

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INTRODUCTION

Ovarian cancer is the second most common gynecologic malignancy with 20 180 new cases and 15 310 deaths each year in women in the USA (1). The standard treatment for ovarian cancer consists of staging laparotomy, including maximal cytoreductive surgery and adjuvant chemotherapy

using taxanes and platinum compounds. As a result of prospective trials by the Gynecologic Oncology Group (GOG) and European–Canadian investigators, paclitaxel and cisplatin became a more effective regimen in 1998 (2). However, carboplatin has been the preferred agent to cisplatin because gastrointestinal and neurological toxicities of carboplatin were appreciably lower than those of cisplatin in some studies, including the GOG protocol 158 (3).

The number of cycles of intravenous adjuvant paclitaxel and carboplatin seems to be different according to the International Federation of Gynecology and Obstetrics (FIGO) criteria for ovarian cancer (4). Treatment with these drugs every 3 weeks for 3–6 cycles is recommended in patients with high-grade, high-risk stage I epithelial ovarian cancer. For those with advanced-stage epithelial ovarian cancer, intravenous adjuvant paclitaxel and carboplatin every 3 weeks for 6–8 cycles is recommended (5).

Although ~50% of patients with advanced-stage epithelial ovarian cancer achieve a first pathologic complete remission with the first treatment course, 90% of suboptimally debulked patients and 70% of optimally debulked patients relapse in 18–24 months. Improvement of survival should be approached by making primary adjuvant chemotherapy more effective or by applying consolidation therapy to patients with complete response after primary standard treatment (6).

Nevertheless, the role of consolidation chemotherapy is controversial in advanced-stage epithelial ovarian cancer patients with complete response after primary standard treatment. Some studies have shown that consolidation chemotherapy improves survival in patients with complete response to paclitaxel- and platinum-based chemotherapy (7,8). On the other hand, consolidation chemotherapy has been reported to be ineffective for patients with complete response and increases the incidence of chemotherapy-induced toxicities, including peripheral neuropathy (9,10). Furthermore, the role of consolidation chemotherapy has not yet been completely clarified because previous studies were performed with various methods of consolidation chemotherapy including different routes of administration (intravenous or intraperitoneal), different regimens of chemotherapy and concurrent radiation therapy.

Therefore, this study was designed to evaluate the efficacy of three additional cycles of intravenous chemotherapy using paclitaxel/carboplatin as consolidation chemotherapy in patients with advanced-stage epithelial ovarian cancer who achieved complete response after six cycles of the same chemotherapy.

MATERIALS AND METHODS

Patients

All data of patients for this study were derived from a database of 477 patients who were diagnosed with epithelial ovarian cancer after staging laparotomy between January 1997 and March 2007. The inclusion criteria were as follows: patients with a histological confirmation of epithelial ovarian cancer; those who underwent staging laparotomy including maximal cytoreductive surgery; those treated with adjuvant paclitaxel and carboplatin chemotherapy for six or nine cycles; those with complete response after six cycles of paclitaxel and carboplatin chemotherapy; Eastern Co-operative Oncology Group performance states of 0 to 2; and those without any underlying diseases that may have affected survival. The current study was approved by the Institutional Review Board of Seoul National University Hospital. The requirement for informed consent was waived because of the retrospective nature of this study.

Patients were required to have adequate bone marrow, hepatic and renal function, defined as white blood cells $\geq 3000/mm^3$, absolute neutrophil counts $\geq 1500/mm^3$, platelet counts $\geq 75\,000/mm^3$, hemoglobin levels ≥ 8.0 g/dl, serum bilirubin levels ≤ 1.8 mg/dl, serum transaminase levels ≤ 100 IU/l and serum creatinine levels ≤ 1.5 mg/dl.

Optimal and suboptimal debulking surgeries were defined as a residual tumor ≤ 1 cm and >1 cm in maximal diameter, respectively. All patients were classified according to the FIGO criteria for ovarian cancer (4), and histological diagnosis was performed according to the World Health Organization (WHO) classification.

All patients were then divided into two groups. Patients were similarly informed of their eligibility to receive three additional cycles of consolidation chemotherapy; patient consent to treatment was included in the medical records. Patients who then received three additional cycles after six cycles of primary adjuvant chemotherapy were included in Group 1, whereas patients treated with only six cycles of adjuvant chemotherapy were included in Group 2.

Chemotherapy

All patients received intravenous adjuvant paclitaxel and carboplatin chemotherapy that started 2–3 weeks after surgery. The chemotherapeutic regimens consisted of paclitaxel (135 mg/m^2 for a 24-h infusion period or 175 mg/m^2 for a 3-h infusion period) and carboplatin (AUC 4.5 or 5). Chemotherapy was repeated every 3 weeks.

Evaluation of Response, Definition of Survival and Toxicity Criteria

Responses after six cycles of primary adjuvant chemotherapy were evaluated using appropriate imaging studies, such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET), and serum CA-125 levels. Serum CA-125 levels were measured within 1 week before staging laparotomy and each cycle of primary adjuvant chemotherapy. They were measured using a radio-immunoassay kit (Fujirebio Diagnostics, Malvern, PA, USA) (11). The upper normal value of serum CA-125 was 37 U/ml. Since second-look laparotomy has been reported to be not associated with improvement in clinical outcomes (3),

response to the chemotherapy was defined in relation to the difference between baseline and 4 weeks after the completion of chemotherapy according to the Response Evaluation Criteria in Solid Tumors (RECIST) and serum CA-125 levels (12,13). Therefore, a complete response was defined as the disappearance of all measurable diseases for at least 4 weeks and the normalization of serum CA-125 levels after five cycles of the chemotherapy.

Disease-free survival (DFS) was defined as the time that elapsed from the date after the completion of primary adjuvant chemotherapy to the date of clinically proven recurrence. Overall survival (OS) was calculated as the time from the date of staging laparotomy to the date of cancer-related death or the end of study. Hematological toxicities due to chemotherapy were coded according to the National Cancer Common Toxicity Criteria (NCI-CTC), version 2.0 (14).

STATISTICAL ANALYSIS

Clinical prognostic factors affecting DFS and OS were identified by the use of Cox's proportional hazard analysis. DFS and OS between the two groups were evaluated using the Kaplan–Meier method with the log-rank test. Clinical characteristics and hematological toxicities were analysed using the Student's t-test and chi-square test. Statistical analyses were performed using SPSS software (Version 12.0; SPSS Inc, Chicago, IL, USA). A value of $P < 0.05$ was considered statistically significant.

RESULTS

PATIENTS CHARACTERISTICS

A total of 94 patients with a median age of 52 years (range, 24–79 years) were enrolled in the current study. Among all patients, 57 were included in Group 1 and 37 in Group 2. Clinicopathologic characteristics of the two groups are summarized in Table 1. Sixty-two (66.0%) patients were in menopause. According to the FIGO criteria for ovarian cancer, two (2.1%) patients were in Stage IIIa, 11 (11.7%) in Stage IIIb, 73 (77.7%) in Stage IIIc and 8 (8.5%) in Stage IV. Tumor grade was G1 in 9 (9.6%), G2 in 17 (18.1%) and G3 in 68 (72.3%) of all patients. Histologically, 77 (81.9%) tumors were diagnosed as serous carcinoma, nine (9.6%) as endometrioid carcinoma, five (5.3%) as clear cell carcinoma, one (1.1%) as undifferentiated carcinoma and two (2.1%) as mixed serous and undifferentiated carcinoma.

The median value of serum CA-125 levels before surgery and after six cycles of primary adjuvant chemotherapy were 765 U/ml (range, 21–300 000 U/ml) and 8 U/ml (range, 5–37 U/ml), respectively. Pelvic or para-aortic lymph node sampling or dissection was performed on 54 (57.4%) of all patients, and lymph node metastasis was identified in 31 (57.4%). Among all patients, 48 (51.1%) and 46 (48.9%) patients were classified into optimal and suboptimal groups, respectively. CT was performed in 63 (67.0%) patients, MRI

Table 1. Clinicopathologic characteristics of Groups 1 (nine cycles) and 2 (six cycles)

| Characteristics	Group 1 ($n = 57$)	Group 2 ($n = 37$)	P value
Age (mean $\pm$ SD, year)	51.0 $\pm$ 9.7	56.3 $\pm$ 10.1	0.012
Menopause (n, %)	36 (63.2)	26 (70.3)	0.477
FIGO stage (n, %)			0.078
IIIa−b	5 (8.8)	8 (21.6)	
IIIc−IV	52 (91.2)	29 (78.4)	
Grade (n, %)			0.188
1	8 (14.0)	1 (2.7)	
2	10 (17.5)	7 (18.9)	
3	39 (68.4)	29 (78.4)	
Pathology (n, %)			0.473
Serous	48 (84.2)	29 (78.4)	
Non-serous*	9 (15.8)	8 (21.6)	
Residual tumor (n, %)			0.083
≤1 cm	25 (43.9)	23 (62.2)	
>1 cm	32 (56.1)	14 (37.8)	
Lymph node involvement (n, %)			0.475
Yes	23 (40.4)	8 (21.6)	
No	15 (26.3)	8 (21.6)	
Imaging study for the diagnosis of complete response (n, %)		0.598	
CT	36 (63.2)	27 (73.0)	
MRI	5 (8.8)	2 (5.4)	
PET-CT	16 (28.1)	8 (21.6)	
Serum CA-125 levels after six cycles of chemotherapy (median with range, U/ml)	8 (5, 37)	7 (5, 36)	0.689

*Non-serous: endometrioid adenocarcinoma (nine cases), clear cell carcinoma (five cases), undifferentiated adenocarcinoma (one case), mixed serous and undifferentiated adenocarcinoma (two cases).
CT, computed tomography; FIGO, International Federation of Gynecology and Obstetrics; MRI, magnetic resonance imaging; PET, position emission tomography; SD, standard deviation.

in 7 (7.5%) and PET scan in 24 (25.5%) for the diagnosis of complete response. When clinical characteristics between the two groups were compared using the Student's t-test and chi-square test, there was a significant difference only in age ($P = 0.012$) (Table 1).

EVALUATION OF SURVIVAL AND TOXICITY

The median DFS and OS of all patients was 22 months (range, 1–96 months) and 74 months (range, 6–100 months), respectively. The median DFS in Groups 1 and 2 was 15 and 22 months, respectively ($P = 0.703$) (Fig. 1). We calculated mean OS in the two groups because Group 2 did not reach median OS. The mean OS in Groups 1 and 2 was
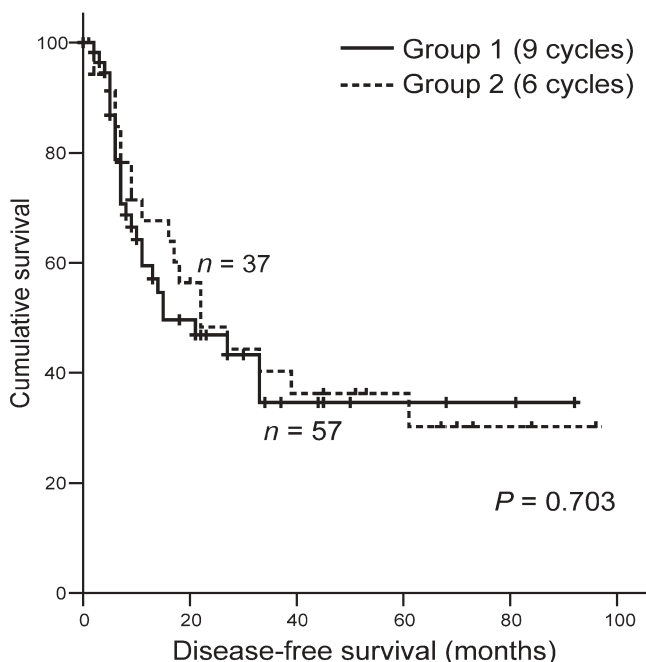
Figure 1. Kaplan–Meier analysis with the log-rank test of disease-free survival (DFS) between groups 1 (9 cycles) and 2 (6 cycles) (median DFS: 15 versus 22 months, $P = 0.703$).
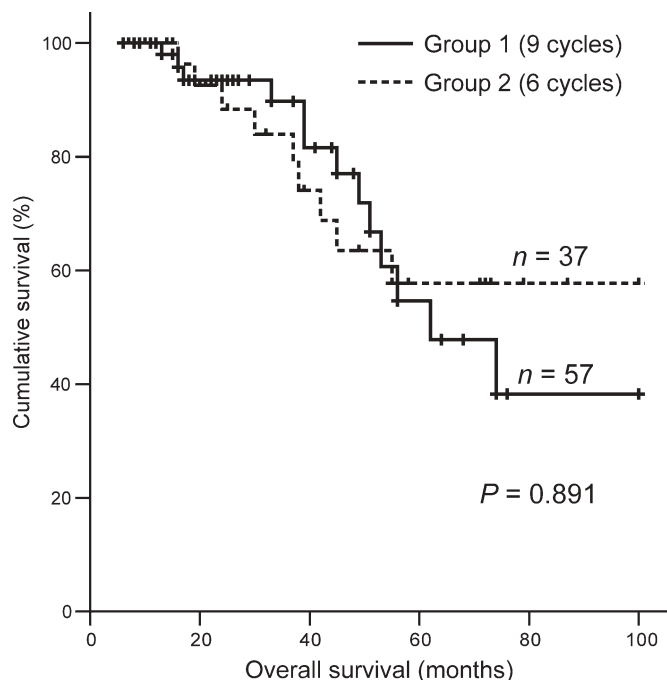
Figure 2. Kaplan–Meier analysis with the log-rank test of overall survival (OS) between groups 1 (9 cycles) and 2 (6 cycles) (mean OS: 69 versus 73 months, $P = 0.891$).

69 and 73 months, respectively ($P = 0.891$) (Fig. 2). On multivariate Cox's proportional hazard analysis, consolidation chemotherapy was not a prognostic factor for DFS although optimal debulking surgery and lower value of

Table 2. Multivariate Cox's proportional hazard analysis for clinical prognostic factors affecting disease-free survival (DFS) of patients with complete response after six cycles of primary adjuvant paclitaxel and carboplatin following staging laparotomy in advanced-stage epithelial ovarian cancer

Characteristics	Hazard ratio	95% confidence interval	P value
Age (year)			
<50	Reference		
≥ 50	1.319	0.538–3.231	0.545
FIGO stage			
IIIa–b	Reference		
IIIc–IV	0.420	0.063–2.803	0.370
Grade			
1	Reference		
2	1.706	0.277–10.514	0.565
3	2.691	0.564–12.850	0.214
Histology			
Serous	Reference		
Non-serous*	2.241	0.577–8.699	0.243
Primary adjuvant chemotherapy (cycles)			
6	Reference		
9	0.631	0.121–3.292	0.585
Residual tumor (cm)			
≤ 1	Reference		
>1	6.195	1.631–23.528	0.007
Lymph node involvement			
No	Reference		
Yes	1.895	0.591–6.074	0.282
Serum CA-125 levels after six cycles of primary adjuvant chemotherapy	1.127	1.045–1.217	0.002

*Non-serous: endometrioid adenocarcinoma (nine cases), clear cell carcinoma (five cases), undifferentiated adenocarcinoma (one case), mixed serous and undifferentiated adenocarcinoma (two cases).

serum CA-125 levels after six cycles of primary adjuvant chemotherapy were independent prognostic factors improving DFS ($P < 0.05$) (Table 2). However, there was no independent prognostic factor for OS ($P > 0.05$).

When chemotherapy-induced hematological toxicities were compared between the two groups, Grade 3 or 4 leukopenia was more common in patients who were treated with consolidation chemotherapy than in those who were not (50.9 versus 21.6%, $P = 0.004$) (Table 3).

DISCUSSION

The aim of the current study was to evaluate the efficacy of three additional cycles as consolidation therapy for advanced-stage epithelial ovarian cancer patients with

Table 3. Chemotherapy-induced hematological toxicities between Groups 1 (nine cycles) and 2 (six cycles)

Chemotherapy-induced hematologic toxicity	Group 1 ($n = 57$)	Group 2 ($n = 37$)	P value
Anemia (n, %)			0.973
Grade 0–2	49 (86.0)	31 (83.8)	
Grade 3–4	8 (14.0)	6 (16.2)	
Leukopenia (n, %)			0.004
Grade 0–2	28 (49.1)	29 (79.4)	
Grade 3–4	29 (50.9)	8 (21.6)	
Neutropenia (n, %)			0.396
Grade 0–2	8 (14.0)	9 (24.3)	
Grade 3–4	49 (86.0)	28 (75.7)	
Thrombocytopenia (n, %)			0.628
Grade 0–2	55 (96.5)	34 (91.9)	
Grade 3–4	2 (3.5)	3 (8.1)	

complete response after six cycles of adjuvant paclitaxel and carboplatin chemotherapy after staging laparotomy. Consolidation chemotherapy using paclitaxel/carboplatin may be inefficient and relatively toxic to advanced-stage epithelial ovarian cancer patients with complete response to six cycles of the same chemotherapy after surgery. The current study included some limitations as follows: first, the recommendation of additional chemotherapy in complete responders' after six cycles of adjuvant paclitaxel/carboplatin chemotherapy was different depending upon the physician because the role of consolidation chemotherapy has been controversial in previous studies. Thus, patients were classified into two groups based upon patient consent to additional consolidation chemotherapy; all patients were similarly informed of their eligibility for additional chemotherapy but classification was based upon the individual patient's decision. Secondly, the number of serous-type epithelial ovarian cancer is relatively higher than that suggested in a previous report (52.4%) although serous type is known to be the most frequent in epithelial ovarian cancer (15). Thirdly, different imaging studies (CT, MRI or PET) were used for the evaluation of complete response. However, there was no significant difference in the distribution of selected types of imaging studies, and survival was not affected by the type of imaging studies between the two groups ($P > 0.05$), which minimized the bias in the current study.

The reason why consolidation chemotherapy has been important for the management of epithelial ovarian cancer is that most clinicians expect that extending treatment beyond the standard six cycles of chemotherapy can improve survival in epithelial ovarian cancer. Thus, various methods have been developed, which consist of different regimens using paclitaxel or platinum agents (8,16,17), second-line chemotherapy (18,19), intraperitoneal chemotherapy (20,21), high-dose chemotherapy with hematopoietic support (22) and whole abdominal radiotherapy (23).

Nevertheless, no randomized trial with regard to consolidation chemotherapy has provided a statistically significant improvement in OS although a small number of phase II studies have suggested improved outcomes (24,25). The only randomized trial with the evidence of clinical benefit was reported by the Southwest Oncology Group/GOG study of ovarian cancer patients receiving 3 versus 12 additional cycles of intravenous paclitaxel following a complete response to platinum and paclitaxel chemotherapy. The study showed a progression-free survival (PFS) advantage of 28 versus 21 months in favor of the 12-cycle arm (hazard ratio = 2.31; 95% confidence interval = 1.08–4.94; $P = 0.005$). Although survival data were not available because of its early termination by the data safety monitoring committee, there was no difference in OS between the treatment arms as of the date of study closure (17).

The current study demonstrated that consolidation chemotherapy using three additional cycles comprised the best regimen (intravenous paclitaxel and carboplatin), as primary adjuvant chemotherapy did not improve DFS and OS in patients with advanced-stage epithelial ovarian cancer, but who achieved complete response after six cycles of the same regimen, supporting the results of previous reports with regard to the uselessness of consolidation chemotherapy. In a similar study, three cycle consolidation chemotherapy with paclitaxel and platinum-based chemotherapy did not provide a favorable outcome in epithelial ovarian cancer patients with complete response (26).

Moreover, consolidation chemotherapy may increase toxicities in patients with complete response after primary standard therapy. Consolidation chemotherapy using weekly paclitaxel increased the risk for the development of severe peripheral neuropathy when it was administered for 3–12 cycles (9). Three additional cycles of paclitaxel- and platinum-based chemotherapy increased Grade 3 or 4 toxicities in patients with complete response after primary treatment although it was statistically insignificant (26). In the current study, there was a significant increase of Grade 3 or 4 leukopenia in patients who underwent consolidation chemotherapy ($P = 0.004$).

In conclusion, prolonged use of the preferred chemotherapeutic regimen using paclitaxel and carboplatin may not improve survival in patients with advanced-stage epithelial ovarian cancer who achieved complete response after six cycles of the same chemotherapy, and may increase hematological toxicities, such as Grade 3 or 4 leukopenia.

Conflict of interest statement

None declared.

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