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A Phase II Study of Paclitaxel and Carboplatin with a Biweekly Schedule in Patients with Epithelial Ovarian Cancer: Gynecologic Cancer Network Trial

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Abstract

Aim: The objective of this multicenter phase II study was to evaluate the effects of biweekly paclitaxel and carboplatin combination chemotherapy on response rate and toxicities in patients with epithelial ovarian cancer.

Patients and Methods: Patients with International Federation of Gynecology and Obstetrics stage II to IV ovarian cancer received paclitaxel at a dose of 120 mg/m^2 and carboplatin at an area under the curve of 3 mg/mL per minute every 2 weeks for 8 or more cycles. Inclusion criteria included an Eastern Cooperative Oncology Group performance status of 0 to 2 and no previous chemotherapy. Informed consent was obtained from each patient before the start of treatment.

Results: From March 2003 through July 2009, 42 patients from 5 institutions were eligible to be evaluated for response and toxicity. The median age was 60.5 years (age range, 34–81 years). The International Federation of Gynecology and Obstetrics stage was stage II in 3 patients, stage III in 31 patients, and stage IV in 8 patients. The response rate was 66.7% (95% confidence interval: 50.5%–80.4%). Sixty-nine percent (29 of 42) of patients received 8 or more cycles of chemotherapy. The median progression-free survival was 18.5 months, and overall survival was 59.1 months. The most common grade 3 or 4 hematological toxicity was neutropenia (61.0%). No patients had grade 3 or 4 thrombocytopenia. The most common grade 3 nonhematological toxicities were neuropathy (4.9%) and nausea (2.4%).

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Conclusion: Paclitaxel combined with carboplatin using a biweekly schedule is a safe and effective chemotherapy regimen for patients with epithelial ovarian cancer. Our results suggest that a biweekly schedule is well tolerated and is less toxic than a triweekly schedule.
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Key words: phase II study, paclitaxel, carboplatin, biweekly schedule, ovarian cancer

Introduction

The standard initial treatment for advanced ovarian cancer is primary surgery followed by adjuvant chemotherapy. In patients with advanced epithelial ovarian cancer, paclitaxel and carboplatin given every 3 weeks is considered the standard first-line chemotherapy regimen[1]. However, in Japanese patients treatment with paclitaxel (175 mg/m^2) combined with carboplatin (at an area under the curve [AUC] of 5 mg/mL per minute) every 3 weeks is associated with high rates of grade III and IV hematological and nonhematological toxicities[2]. Recently, the concept of dose-dense therapy has led to the administration of paclitaxel in smaller divided doses and has expanded treatment possibilities[3-6]. However, in clinical trials in patients with breast cancer, the incidence of neurotoxicity is higher when paclitaxel is given every week than when given every 3 weeks[7].

We have previously performed a phase I study (dose-finding study) of paclitaxel in combination with carboplatin given every 2 weeks in patients with epithelial ovarian cancer[4]. A main aim of a biweekly schedule is to decrease paclitaxel/carboplatin-related toxicity. In our previous phase I study, different doses of biweekly paclitaxel and carboplatin were analyzed to define the dose-limiting toxicities and the maximal tolerated dose of this new regimen[4]. In that study, the recommended dose of paclitaxel for a phase II study was 120 mg/m^2 on day 1 with carboplatin at an AUC of 3, every 2 weeks[4].

The present phase II trial was designed to evaluate the safety and effectiveness of paclitaxel combined with carboplatin using a biweekly schedule as a chemotherapy regimen in patients with epithelial ovarian cancer.

Materials and Methods

Eligibility

All patients had undergone primary surgery with the aim of maximal tumor reduction. Patients started initial chemotherapy within 3 weeks of primary surgery. Eligibility criteria were: 1) a histologically proven diagnosis of International Federation of Gynecology and Obstetrics stage II to IV epithelial ovarian cancer[8]; 2) at least 1 measurable target lesion according to the Response Evaluation Criteria in Solid Tumors[9]; 3) an Eastern Cooperative Oncology Group performance status of 0 to 2[10]; 4) no previous chemotherapy or radiotherapy; 5) adequate main organ functions (defined as a white blood cell count ≥4,000 and ≤12,000/μL, hemoglobin ≥9.5 g/dL, platelet count ≥100,000/μL, bilirubin ≤1.5 mg/dL, asparate aminotransferase and alanine aminotransferase ≤2.0 times the upper limit of normal, serum creatinine ≤1.5 mg/dL, creatinine clearance ≥ 60 mL / minute, and a normal electrocardiogram [no abnormalities requiring treatment]); 5) life expectancy greater than 3 months; 6) no severe concurrent disease; 7) age of 20 years or greater; and 8) the ability to give written informed consent to participate in this study.

Exclusion criteria were a past or present history of drug allergy, significant cardiac disease, pulmonary fibrosis, massive pleural effusion, preexisting sensory or motor neuropathy, another malignancy, hypersensitivity to preparations containing polyoxyethylene castor oil (e.g., cyclosporine preparations) or hardened castor oil (e.g., injectable vitamin preparations), acute inflammatory disease, confirmed or suspected pregnancy or breastfeeding, symptomatic brain metastasis, or any other condition considered by the

investigator to preclude participation in the present study. Finally, the study protocol was approved by the ethics committees of the participating institutions, and written informed consent was obtained from the patients before the start of treatment. The present study was performed after the protocol had been approved by the institutional review board of each participating center.

Treatment

Patients received paclitaxel intravenously at a dose of 120 mg/m^2 on day 1 in combination with carboplatin (AUC3) every 2 weeks according to the following dose schedule. Paclitaxel at a dose of 120 mg/m^2 was dissolved in 500 mL of 0.9% saline or 5% glucose, was administered intravenously over 90 minutes, and was followed by carboplatin (AUC3), which was infused intravenously over 60 minutes. The dose of carboplatin was calculated with Calvert's formula [mg = targeted AUC × (glomerular filtration rate + 25)][11]. The glomerular filtration rate was estimated from the creatinine clearance as calculated with Jelliffe's formula[12]. Treatment cycles were repeated every 2 weeks for a planned maximum of 8 cycles. Patients who had a complete response (CR) could receive 4 additional cycles of chemotherapy. Patients who had residual disease after 8 cycles of treatment could also receive 4 additional cycles of chemotherapy. All patients were premedicated with dexamethasone (20 mg, i.v.), ranitidine (50 mg, i.v.), and diphenhydramine (50 mg). The dose of paclitaxel was reduced by 20 mg/m^2 when lasting grade 4 myelosuppression or a grade 3 or greater nonhematological toxicity occurred during the previous cycle. Granulocyte colony-stimulating factor was subcutaneously administered when chemotherapy caused a leukocyte count of <2,000/μL or a neutrophil count of <1,000/μL with fever or when it caused a leukocyte count of <1,000/μL or a neutrophil count <500/μL. Administration of a 5HT3-receptor antagonist before chemotherapy was allowed. There was no other premedication or supportive therapy for this regimen. A treatment delay of no more than 2 weeks was allowed.

Both interval debulking surgery after 2 to 6 cycles of chemotherapy and secondary debulking surgery after 8 cycles of chemotherapy were allowed. These procedures were performed within 6 weeks after chemotherapy, and subsequent chemotherapy was restarted within 4 weeks after surgery.

Follow-up Evaluation

Before enrollment, all patients gave a detailed medical history, underwent a complete physical examination, complete blood cell count, and serum chemistry studies, pelvic and abdominal computed tomography, and electrocardiography, and weight, height, and Eastern Cooperative Oncology Group performance status were recorded. Physical examination, symptom evaluation, routine blood tests, and blood biochemistry examination were performed every week during treatment. The objective response was evaluated every 2 months.

The primary endpoint was response rate. Clinical response was assessed in eligible patients with lesions that could be measured in 1 dimension. The assessment of response had to be confirmed on 2 occasions at least 4 weeks apart. The response to treatment, which included CR, partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE), was defined according to the Response Evaluation Criteria in Solid Tumors[9]. Toxicity was evaluated every 2 weeks according to National Cancer Institute-Common Terminology Criteria, version 2.0[13,14].

The secondary endpoints were progression-free survival, overall survival, and adverse events. The planned analyses of progression-free survival and overall survival included data on eligible patients according to the intention-to-treat principle.

Statistical Analysis

Response rates were calculated as relative rates with their 95% confidence intervals (CIs). Progression-free survival was measured from the date of enrollment to the first objective evidence of PD or to the date of death, whichever came first. Overall survival was measured from the date of death. Progression-free survival and overall survival were estimated with the Kaplan-Meier method.

The required sample size was determined with a binominal distribution. Population size was

Table 1 Patient characteristics

Variable	N=42
Median age, years (range)	60.5 (34–81)
FIGO stage	
Ⅱ	3 (7.1%)
Ⅲ	31 (73.8%)
Ⅳ	8 (19.0%)
Performance status (ECOG)	
0 or 1	30 (71.4%)
2	12 (28.6%)
Size of residual tumor after primary surgery	
1.0–2.0 cm	8 (19.0%)
2.1–5.0 cm	15 (35.7%)
5.1–10.0 cm	13 (31.0%)
>10.0 cm	6 (14.3%)
Secondary surgery	
Interval debulking	6 (14.3%)
Secondary debulking	7 (16.7%)
Histological type	
Serous adenocarcinoma	30 (71.4%)
Endometrioid adenocarcinoma	3 (7.1%)
Clear cell carcinoma	4 (9.5%)
Mucinous adenocarcinoma	2 (4.8%)
Other types	3 (7.1%)

FIGO, International Federation of Gynecology and Obstetrics; ECOG, Eastern Cooperative Oncology Group

established for phase II studies with an alpha error of 5% and a beta error of 20% and for an expected response rate of 70%. The threshold of the response rate was 49%. Thus, at least 42 patients had to be enrolled in the study.

Results

Patient Characteristics

A total of 45 patients from 5 institutions were enrolled in this study from March 2003 through July 2009. Although 45 patients were enrolled, 3 had no measurable target disease, therefore, 42 patients met the entry criteria (**Table 1**). The median age was 60.5 years (range: 34–81 years). Thirty patients (71.4%) had a performance status of 0 or 1. All patients had residual lesions measuring more than 1 cm in diameter after primary surgery. Six of the 42 patients (14.3%) had undergone interval debulking surgery, and 7 (16.7%) had undergone secondary debulking surgery. The histologic diagnoses were serous adenocarcinoma in 30 patients (71.4%), endometrioid adenocarcinoma in 3 patients (7.1%), clear cell carcinoma in 4 patients (9.5%), mucinous adenocarcinoma in 2 patients (4.8%), and other types of tumor in 3 patients (7.1%).

Treatment Summary

The numbers of patients treated at each cycle of treatment were as follows: 1 cycle, 2 patients; 2 cycles, 2 patients; 3 cycles, 3 patients; 5 cycles, 1 patient; 6 cycles, 4 patients; 7 cycles, 1 patient; 8 cycles, 17 patients; 10 cycles, 9 patients; 11 cycles, 1 patient; and 12 cycles, 2 patients. Of the 42 eligible patients, 29 (69%) received 8 or more cycles of treatment, and 13 (31%) received fewer than 8 cycles. The most common reason for discontinuation of treatment was toxicity (4 of 13 patients, 31%). The median number of treatment cycles received was 8 (range: 1–12), and the median duration of treatment was 105 days (range: 1–224). The dose of paclitaxel was reduced in 11 patients (26%) because of hematological toxicity, such as neutropenia (26%), or peripheral neuropathy.

Efficacy

On intention-to-treat analysis, 8 patients (19.1%) had CR, 20 (47.6 %) had PR, 5 (11.9%) had SD, 4 (9.5%) had PD, and 5 (11.9%) had NE (**Table 2**). The overall response rate was 66.7% [95% CI: 50.5%–80.4%]. The disease control rate (CR + PR + SD) was 78.6%. The overall response rate and the disease control rate in patients with serous adenocarcinoma of the ovary (30 of 42 patients, 71.4%) were 70.0% and 83.3%, respectively, and in patients with clear cell adenocarcinoma (4 of 42 patients, 9.5%) were 25.0% and 25.0%, respectively (**Table 3**).

When analyzed in August 2010, after a median duration of follow-up of 24.9 months, the median overall survival was 59.1 months and the median progression-free survival was 18.5 months (**Fig. 1**).

Toxicity

The most common hematological toxicity of grade 3 or 4 was neutropenia (60.9%; **Table 4**). However, there was no febrile neutropenia and no grade 3 or 4 thrombocytopenia. Granulocyte colony-stimulating factor was administered to 69.0% of patients. The grade 3 nonhematological toxicities were neuropathy in 2 patients (4.8%) and nausea in 1 patient (2.4%). Neuropathy occurred in 16 patients (38.1%) but was grade 1 in 13 (31.0%) of them. Other toxicities included fatigue (43.8%), nausea (36.5%), myalgia (22.0%), and arthralgia (21.9%). There were no treatment-related deaths.

Table 2 Clinical response (N=42)

	N	%
Complete response	8	19.1
Partial response	20	47.6
Stable disease	5	11.9
Progressive disease	4	9.5
Not evaluable	5	11.9
Response rate	28	66.7
95% Confidence interval		50.5–80.4
Disease control rate	33	78.6

Disease control rate: Complete response+Partial response+Stable disease

Discussion

In the present study, we made 3 important clinical observations. First, the response rate of patients with epithelial ovarian cancer to biweekly paclitaxel and carboplatin combination chemotherapy was 66.7%. Second, the most common adverse events were neutropenia and neuropathy. Third, the median overall survival was 59.1 months, and the median progression-free survival was 18.5 months.

First, the response rate of patients with epithelial ovarian cancer to biweekly paclitaxel and carboplatin combination chemotherapy was 66.7%. In the present study, 28 of 42 patients had CR or PR (66.7%; 95% CI, 50.5%–80.4%). This response rate was equivalent to those in phase II studies of triweekly paclitaxel plus carboplatin (66.7% to 82%)[2,15]. Clear cell adenocarcinoma of the ovary generally has low sensitivity to chemotherapy and a poor prognosis[16]. In the present study, the response rate of patients with serous adenocarcinoma of the ovary was 70.0%, but that of patients with clear cell adenocarcinoma of the ovary was only 25.0%. This low response rate suggests that a new chemotherapy regimen is necessary to treat clear

Table 3 Response according to histological type (N=42)

Histological type	Response					RR (%)	DCR (%)
	CR	PR	SD	PD	NE		
Serous	5	16	4	1	4	70.0	83.3
Endometrioid	1	1	1			66.7	100.0
Clear cell		1		3		25.0	25.0
Mucinous	1	1				100.0	100.0
Other types	1	1			1	66.7	66.7
Total	8	20	5	4	5	66.7	78.6

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable RR, response rate; DCR, disease control rate

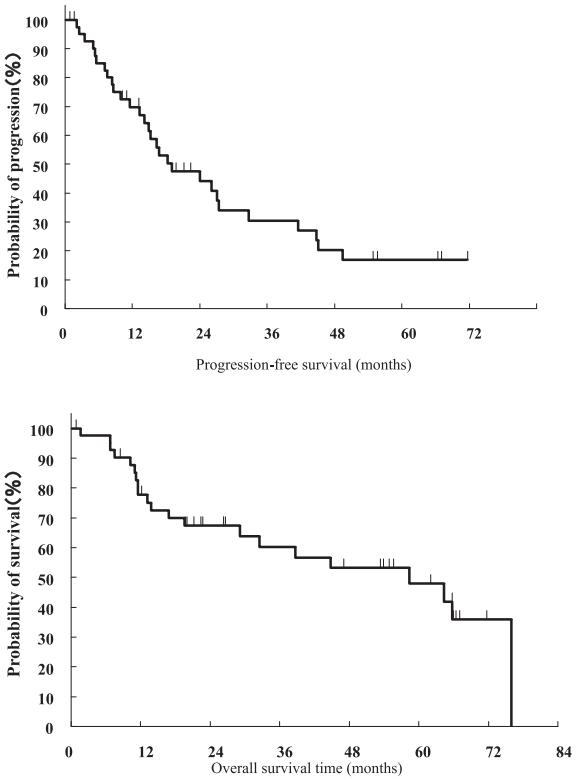

Fig. 1 Progression-free survival (the upper half of the figure) and overall survival (the lower half of the figure) in 42 eligible patients

Table 4 Most severe hematological and nonhematological toxicities (National Cancer Institute Common Toxicity Criteria, version 2)

	Grade (%)			
	1	2	3	4
Neutropenia	4.8	22.0	34.1	26.8
Thrombocytopenia	17.1	2.4	0	0
Anemia	34.1	26.8	2.4	0
Febrile neutropenia	-	-	0	0
Nausea	31.7	4.8	2.4	0
Vomiting	9.8	2.4	0	0
Diarrhea	2.4	0	0	0
Fatigue	39.0	4.8	0	0
Arthralgia	19.5	2.4	0	0
Myalgia	22.0	0	0	0
Neuropathy (motor)	0	0	2.4	0
Neuropathy (sensory)	31.0	2.4	2.4	0

cell adenocarcinoma of the ovary.

Second, the most common adverse events of grade 3 or 4 were neutropenia and neuropathy. Although 60.9% of our patients had grade 3 or 4 neutropenia, no patients had neutropenic fever. Furthermore, the incidence of grade 3 or 4 neutropenia was lower than in studies of paclitaxel and carboplatin administered on a triweekly schedule[2,17]. No cases of grade 3 or 4 thrombocytopenia were observed; this benefit is characteristic of a biweekly regimen. Generally, despite its rarity, thrombocytopenia was a dose-limiting toxicity in the paclitaxel-carboplatin regimen. Prolonged thrombocytopenia would be completely or partially responsible for the cycle delays. These mild hematological toxicities are advantages of this biweekly schedule. Non-hematological toxicity was also mild. The incidence of grade 2 or more neuropathy was only 7.2% and was lower than in previous studies of paclitaxel and carboplatin therapy with a triweekly or a weekly schedule (12.5%[17] to 31.8%[3]).

Third, the median overall survival was 59.1 months, and the median progression-free survival was 18.5 months. The median overall survival was in the range found in previous studies of paclitaxel and carboplatin therapy with a triweely or a weekly schedule (43.3 months[18] to 45.0 months[3]). The median progression-free survival in the present study (18.5 months) was similar to that in studies of paclitaxel plus carboplatin with a conventional triweekly schedule (17.2 months)[18]. However, our median progression-free survival was shorter than that in a German phase II study of paclitaxel and carboplatin with a weekly schedule (22.0 months)[3]. A possible reason for our shorter survival is differences in the patient populations. For example, in our study all patients had residual tumors larger than 1 cm after the primary operations. This high rate of residual disease may have decreased the progression-free survival in our study.

In conclusion, paclitaxel combined with carboplatin using a biweekly schedule is a safe and effective chemotherapy regimen for patients with epithelial ovarian cancer. Our results suggest that a biweekly schedule is well tolerated and is less toxic than a triweekly schedule.

Conflict of Interest: The authors declare that they have no conflicting interests.

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