Phase II Study of Carboplatin and Weekly Irinotecan Combination Chemotherapy in Recurrent Ovarian Cancer: A Kansai Clinical Oncology Group Study (KCOG0330)

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Abstract. *Background: A multicenter phase II trial was conducted to evaluate the efficacy and toxicity of irinotecan plus carboplatin chemotherapy in patients with epithelial ovarian cancer (EOC). Patients and Methods: Patients with either radiologically- or serologically-recurrent EOC were administered intravenous irinotecan (60 mg/m^2; days 1 and 8) and carboplatin area under the curve of 5 mg/ml/min (day 1), repeated every 21 days. The primary end-point was response rate (RR), while the secondary end-points were adverse events and progression-free survival (PFS). Results: Between 2005 and 2009, 40 patients (median age=59 years) with EOC were enrolled. Intention-to-treat analysis showed an RR of 43% [95% confidence interval (CI)=27-58%]. For patients with a platinum-free interval (PFI) of <6 months, overall RR based on RECIST was 21% (95% CI=0-43%) and median PFS was 3.7 months (95% CI=2.5-7.7 months), while those in patients with PFI ≥6 months were 52% (95% CI=31-74%) and 9.1 months (95% CI=7.9-11.2 months), respectively. Grade 3/4 toxicity encountered during the first cycle included G3/G4 neutropenia in 65% of patients (12/14), G3/G4 thrombocytopenia in 48% (18/1), G3 febrile neutropenia in 5% (2), G3 nausea in 5% (2), G3 diarrhea in 5% (2), and G3 fatigue in 5% of patients (2). Conclusion: This carboplatin plus irinotecan combination demonstrated a modest activity in recurrent EOC. However, considering its hematological toxicities, the regimen should be further investigated to establish the feasibility of the modified dose for platinum-sensitive disease.*

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Most patients present with advanced disease at the initial diagnosis of ovarian cancer, and in more than 65% of cases, relapse occurs within two years (1). Relapse occurring within six months after platinum-based chemotherapy is generally defined as platinum-resistant disease, whereas relapse after six months is defined as platinum-sensitive disease. The standard treatment for patients with platinum-resistant disease is non-platinum monotherapy because previous reports have shown no survival merit and increased toxicity with non-platinum combination therapy (2, 3). However, a retrospective study conducted in 2003 showed that patients who showed relapse within six months of prior therapy and then received platinum-based combination chemotherapy had a higher response rate (RR) and increased progression-free (PFS) and overall survival (OS) (4). Therefore, platinum-based chemotherapy was considered to be effective for patients with relapse within six months. The standard treatment for patients with platinum-sensitive disease is combination chemotherapy including carboplatin, although artificial prolongation of the platinum-free interval (PFI) is controversial (5, 6). In combination with carboplatin, cytotoxic agents such as paclitaxel, gemcitabine, or pegylated liposomal doxorubicin (PLD), are generally used (7-9).

Irinotecan is a water-soluble derivative of camptothecin that inhibits the nuclear enzyme topoisomerase-I and interferes with DNA replication and cell division. Additionally, the combination of cisplatin and irinotecan has shown synergistic effects *in vitro* (10-12), while a phase I trial demonstrated the efficacy of a combination of irinotecan and carboplatin for patients with ovarian cancer (13). Therefore, we performed a phase II prospective study to

Table I. *Patients' demographics and baseline characteristics (N=40).*

Variable	
Mean age (range), years	59 (33-78)
ECOG PS, n (%)	
0	18 (45)
1	14 (35)
2	8 (20)
Primary site, n (%)	
Epithelial ovarian	38 (95)
Primary peritoneal	2 (5)
Previous regimens, n (%)	
1	19 (49)
2	12 (30)
≥3	9 (22)
PFI, months, n (%)	
≤1	3 (8)
1<PFI <6	14 (35)
6≤PFI <12	11 (28)
≥12	12 (30)
Definition of recurrence, n (%)	
Measurable disease by RECIST	35 (88)
CA125 by GCIG	5 (13)
Histology, n (%)	
Serous (high-grade)	27 (68)
Endometrioid	7 (18)
Other	6 (15)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; PFI, platinum-free interval, interval following the most recent platinum-based chemotherapy; RECIST, Response Evaluation Criteria in Solid Tumors ver. 1.0; GCIG, Gynecologic Cancer InterGroup.

assess the antitumor activity and safety of the combination of carboplatin and irinotecan for patients with recurrent ovarian cancer.

Patients and Methods

Eligibility criteria. Eligible patients were ≥20 years old with a histologically-confirmed diagnosis of epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer; previous platinum and taxane therapy was required. Patients included those with measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0 or CA-125 assessable disease according to Gynecologic Cancer InterGroup (GCIG) criteria. Additional requirements included an Eastern Cooperative Oncology Group performance status of ≤2; life expectancy of at least 12 weeks; and adequate bone marrow, renal, and hepatic function. Exclusion criteria included active infection, uncontrolled diabetes mellitus, severe heart disease, active second malignancy, ileus, or brain metastasis.

Written informed consent was obtained before study participation. The study was approved by the Ethical Review Boards and was conducted in accordance with the Declaration of Helsinki, good clinical practice guidelines, and applicable laws and regulations. The study was additionally approved by the Kansai Clinical Oncology Group (KCOG).

Table II. *Objective and serological responses. ITT, Intention-to-treat analysis; PFI, platinum-free interval.*

Response	ITT	PFI <6 months	PFI ≥6 months
n	40	17	23
RECIST	35	14	21
Complete response	8	1	7
Partial response	6	2	4
Stable disease	12	6	6
Progressive disease	9	5	4
Objective response rate (95% CI)	14/35 40% (24-56)	3/14 21% (0-43)	11/21 52% (31-74)
CA-125	5	3	2
Partial response	3	1	2

Treatment schedule. Eligible patients received 60 mg/m^2 irinotecan by an intravenous drip over 60-90 min on days 1 and 8, and carboplatin at an area under the curve (AUC) of 5 mg/ml/min mg/ml/min intravenously over 60 min following irinotecan on day 1. The carboplatin dose was calculated according to the Jelliffe formula. Dose cycles were repeated every 21 days for a maximum of six cycles in the absence of progressive disease or unacceptable toxicity. The patients were administered antiemetics, including a serotonin antagonist and corticosteroid. All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), ver. 3.0. Cycles could be postponed by up to two weeks due to toxicity; longer toxicity-related delays led to treatment discontinuation. Treatment resumed after recovery from non-hematological (<grade 2 except neuropathy or alopecia) and hematological toxicities [absolute neutrophil count (ANC) ≥1.5×10^9/l and platelet count ≥100×10^9/l). Irinotecan administration on day 8 was omitted if ANC was <1.0×10^9/l, the level of which was amended to <0.75×10^9/l in 2007, or if platelet count was <75×10^9/l. If the patient had grade 4 neutropenia or grade 3 thrombocytopenia for ≥1 day, the chemotherapy dose was reduced during the next cycle to level-1 (AUC 4 mg/ml/min of carboplatin and 50 mg/m^2 of irinotecan) and or level-2 (AUC 4 mg/ml/min of carboplatin and 40 mg/m^2 of irinotecan) following an amendment made in 2007. If a patient had grade 4 neutropenia or grade 3 thrombocytopenia after the dose reduction then they were excluded from the study. If additional dose reductions were required, chemotherapy was discontinued, but the patients were still included in the analysis. If leucopenia or neutropenia had decreased to grade 3 after chemotherapy, granulocyte colony-stimulating factors (G-CSFs) were administered according to the manufacturer's recommendations until the white blood cell and ANC counts recovered.

Study evaluations. Baseline evaluation consisted of a complete history and physical examination that included a gynecological examination, laboratory studies including CA-125 marker analysis, and diagnostic imaging (computed tomography, CT; ultrasonography, US; or magnetic resonance imaging, MRI) within four weeks of study entry. Evaluation before starting treatment at each cycle consisted of a medical history and physical examination, determination of ECOG performance status, complete blood count with differential, creatinine clearance, routine chemistry profiles, and CA-125 analysis.

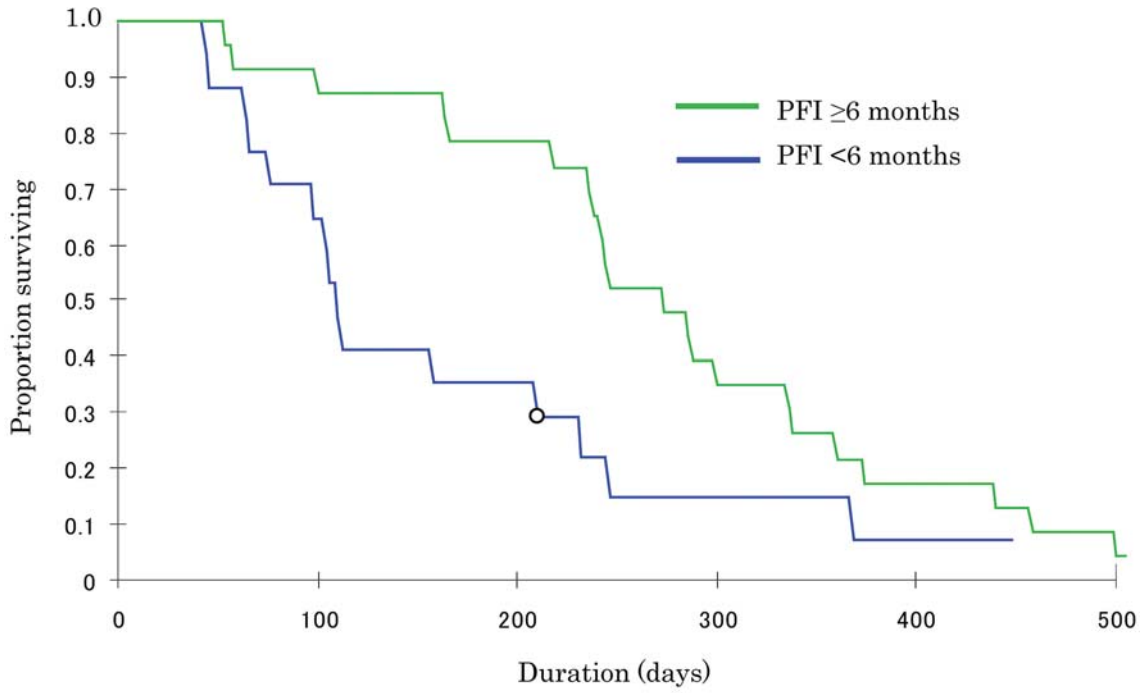

Figure 1. *Kaplan–Meier analysis of PFS among patients with PFI <6 months (n=17) and with PFI ≥6 months (n=23).*

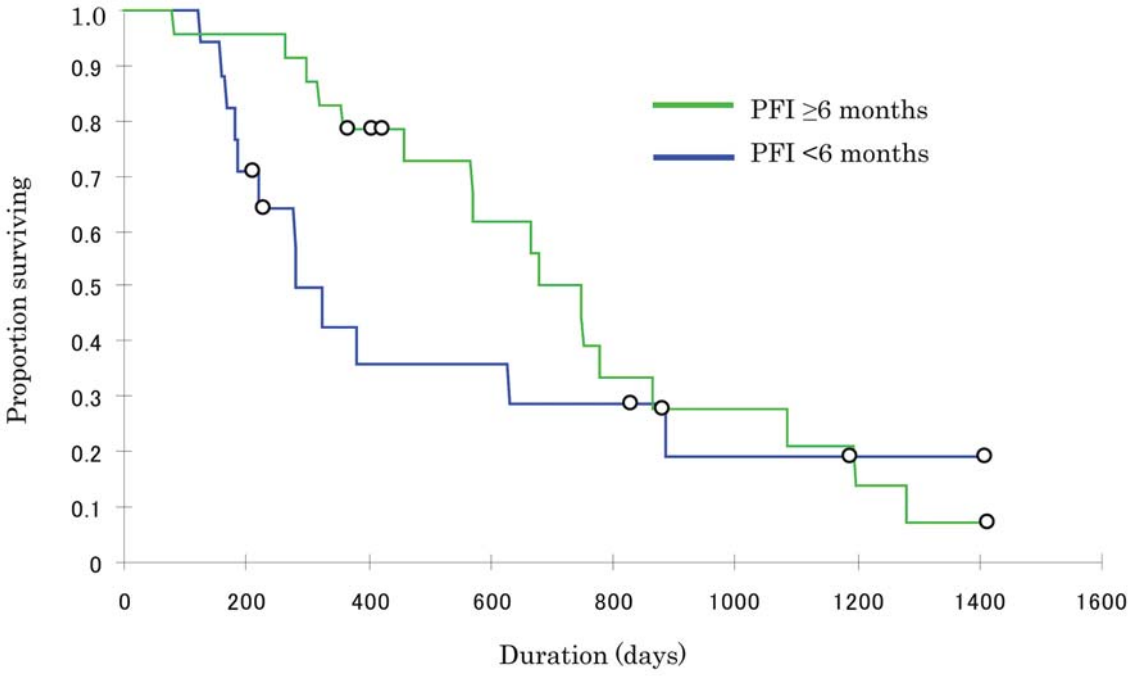

Figure 2. *Kaplan–Meier analysis of OS among patients with PFI <6 months (n=17) and with PFI ≥6 months (n=23).*

Tumor response in patients with measurable disease was checked every 2 cycles and classified according to RECIST, which includes the confirmation of response. Patients who received at least 1 cycle of chemotherapy were assessable for response with CT or MRI scan before every other cycle. Patients who had no measurable disease but displayed elevated CA-125 levels were evaluated according to GCIG criteria. Partial response of CA-125 was defined as a decrease in CA-125 to a level less than half that at baseline for ≥4 weeks.

Table III. *Adverse events. Hematological toxicity (≥grade 3) and non-hematological toxicity (≥grade 2) during the first cycle. *Transfused when platelet levels reached 2.3 and 1.0×10⁴/mm³.*

	No. of patients		(%)
Adverse events	Grade 3	Grade 4	≥Grade 3
Anemia	7	0	7 (18)
Leukopenia	14	7	21 (53)
Neutropenia	14	13	27 (68)
Thromobocytopenia	8	9	17 (43)
Febrile neutropenia	2	0	2 (5)
Transfusion			
Platelets			2* (5)
Packed red blood cells			1 (3)

	No. of patients			
Adverse events	Grade 2	Grade 3	Grade 4	≥Grade 2
Neuropathy-sensory	2	0	0	2
Nausea	2	1	0	3
Fatigue	0	2	0	2
Diarrhea	1	0	0	1
Ileus	0	1	0	1

Table IV. *The proportion of discontinuations after each cycle and reasons for protocol discontinuation. *Both nausea (grade 2) and diarrhea (grade 2) in one patient.*

Protocol discontinuation	No. of patients	%
After each cycle		
1st	12	30
2nd	7	18
3rd	8	20
4th	6	15
5th	0	0
Completed	7	18

Reasons for discontinuation (N=33)	No. of patients	%
Toxicity		
Hematological	15	45
Non-hematological	12	36
Nausea	3*	9
Diarrhea	3*	9
Fatigue	2	6
Ileus	1	3
Anaphylaxis to carboplatin	4	12
Disease progression	4	12
Complete remission	2	6

Toxicities were assessed and graded according to the NCI-CTC ver. 3.0. All patients who had received at least one cycle of chemotherapy were assessable for toxicity and survival. PFS time was defined as the time from the date of study enrollment to the date of objectively determined progressive disease, increased CA-125 level by GCIG criteria, health status deterioration attributable to disease, and death. OS time was defined as the time from the date of study enrollment to death.

Statistical analyses. The investigator-assessed tumor RR, including a 95% two-sided confidence interval (CI), was estimated for the evaluable patients and the intention-to-treat population. This one-stage design tested the null hypothesis that the true RR for this population was equal to 40% compared with the clinically-relevant alternative that the RR was 60%, using alpha=0.05 and beta=0.1 (7). It was determined that 40 patients were required for the trial. Efficacy was assessed in two subgroups of patients: these with a PFI of <6 months and these with a PFI ≥6 months. Analyses were performed on the observed distributions of PFS and OS using the Kaplan–Meier method, including the patients who received the combination of carboplatin and irinotecan with dose modification after discontinuation of the protocol treatment. Toxicity analysis included all patients who received at least one cycle of treatment.

Results

Patients' characteristics. Between March 2005 and January 2009, 40 Japanese women were treated in seven institutions. Among five patients who did not have measurable disease as determined by RECIST, three with PFI <6 months had ascites and two with PFI ≥6 months had retroperitoneal lymph node swelling with elevated serum CA-125 level. Among 17 patients with PFI <6 months, seven had progressed disease during the previous platinum chemotherapy. Among 23 patients with PFI ≥6 months, five had progressed disease during the previous non-platinum chemotherapy. Patients' characteristics are summarized in Table I.

Response rates. Seventeen out of 40 enrolled patients demonstrated a response, and the RR was 43% (95% CI=27-58%); 14 out of 35 patients with measurable disease experienced an objective response, and three out of 5 patients with serological recurrence had a partial response. Subset analyses according to PFI are presented in Table II.

Time-to-event measures. The median follow-up time was 9.3 months (range=4.1-47.1 months) and 19.0 months (range=2.7-47.2 months) for patients with PFI <6 months and ≥6 months, respectively; the median PFS time was 3.7 months (95% CI=2.5–7.7 months) with one patient censored and 9.1 months (95% CI=7.9-11.2 months), respectively (Figure 1). The median OS time was 9.4 months (95% CI=6.3-30.0 months) with 29% censoring, and 25.0 months (95% CI=19.0–28.8 months) with 26% censoring, respectively (Figure 2). Among nine patients with PFI ≤3 months, two (22%) had a PFS of >12 months, and four (44%) and two (44%) patients had OS >24 and >36 months, respectively.

Toxicity. Hematological toxicity was the most common toxicity possibly related to the study drug (Table III). During the first cycle, grade 4 thrombocytopenia was observed in nine patients (23%) and febrile neutropenia occurred in two (5%) patients. Hypersensitivity reaction ≥grade 2 in response to carboplatin was found in four (10%) patients over the course of treatment. The protocol was completed in seven patients (18%), and the median number of cycles was three (Table IV). Twenty-seven patients discontinued treatment because of drug-induced toxicities.

Drug administration. The second cycle was delayed in 28 cases. Actual dose intensity during the first 12 weeks among 21 patients who received the combination chemotherapy for >12 weeks was as follows: median dose of irinotecan, 30.5 mg/m^2/week (range=15-40); median AUC/ week of carboplatin, 1.4 mg (range=1.1-1.7 mg).

Discussion

Planned accrual was generally delayed because the physician was reluctant to recommend a carboplatin combination for patients with PFI <6 months or treatment was not initiated until radiologically-proven or symptomatic recurrence, and secondary surgery was performed for patients with PFI ≥12 months. For the treatment of platinum-resistant disease, RR of up to 30% has been reported in trials of non-platinum monotherapy (14). In phase III trials, the median PFS was about three to four months among patients who received PLD, topotecan, or gemcitabine (15-17). A recent phase III study, AURELIA, showed a median PFS of 3.4 months among control patients who received PLD, topotecan, or weekly paclitaxel (18). Moreover, irinotecan monotherapy showed an RR of 29% and 17 weeks of PFS in a single institute (19). GINECO recently published a study comparing weekly paclitaxel with and without carboplatin; this study demonstrated a trend for prolonged median PFS time in patients treated with carboplatin and paclitaxel (4.8 months) compared with paclitaxel-alone (3.7 months), but the difference was not significant (20). In this trial, the combination of irinotecan and carboplatin had an RR of 21% and 3.7 months of median PFS, with a higher rate of hematological toxicities than that of non-platinum monotherapy. These results do not indicate an advantage of combination chemotherapy.

The efficacy of the current regimen for patients with platinum-sensitive disease was commensurate with other effective carboplatin-based combinations with paclitaxel, gemcitabine, or pegylated doxorubicin (7-9, 21). Neutropenia and thrombocytopenia were the most commonly observed drug-related grade 3 or 4 toxicities. These toxicities also occurred in the phase I study (13). The toxicity profile was similar to that of the combination chemotherapy of carboplatin and gemcitabine (8). In our trial, 27 patients (68%) discontinued treatment because of hematological or non-hematological toxicities. A high rate of discontinuation was due to the strict criteria in this trial compared with those in a phase III trial, which reduced the dose after grade 4 neutropenia lasting >6 days or thrombocytopenia <2.5×10^6/l.

A phase I/II study of topotecan in combination with carboplatin area under the curve of 5 mg/ml min for recurrent platinum-sensitive ovarian cancer also showed hematological toxicities (22). According to the dose-limiting toxicities, the phase II portion was conducted with a topotecan dose of 0.75 mg/m^2 on days 1 to 3, which was lower than the initial dose of topotecan in the phase I portion. RR and median PFS were 67% and 9.5 months, respectively. In this study, phase III investigations were subsequently performed (21). Another phase II study of weekly administration of topotecan with carboplatin showed 40% grade 3/4 neutropenia, 31% RR, and 11 months median PFS (23).

In this trial, among 21 patients who received combination chemotherapy of irinotecan and carboplatin for more than 12 weeks, median actual dose intensities were 30.5 mg/m^2/week of irinotecan and an AUC/week of 1.4 mg for carboplatin. The recommended regimens for further study were 50 mg/m^2 irinotecan on days 1 and 8 and carboplatin AUC of 5 mg/ml/min on day 1, repeated every 21 days, or 50 mg/m^2 irinotecan on days 1, 8, and 15, and a carboplatin AUC of 5 mg/ml min on day 1, repeated every 28 days. The safety of the abovementioned regimens has been reported for patients with small cell lung carcinoma (24-26).

Uridine diphosphate glucuronosyltransferase (UGT) is the principal metabolizing enzyme of irinotecan. There is an interindividual as well as interethnic variability of UGT gene polymorphisms, resulting in diverse toxicities (27-29). During the current study, a personal genetic test to detect the UGT1A1 polymorphism was not conducted. UGT1A1 analysis has been covered by medical insurance since 2008 in Japan, and the adverse events were clinically manageable in all participants. The sample size was small, and weekly low-dose administration of irinotecan, similar to the regimens for standard colorectal cancer (30), might avoid unmanageable adverse events. However, future studies could require genetic tests.

In conclusion, carboplatin and irinotecan combination therapy demonstrated modest activity in the treatment of recurrent ovarian cancer. Myelosuppression was the main toxicity but had a manageable profile. The regimen had to be modified because of delay of the second cycle and the actual dose intensity. The recommended regimen for future studies is carboplatin AUC of 5 mg/ml/min on day 1 in combination with 50 mg/m^2 irinotecan on days 1 and 8 in a three-week course, or on days 1, 8, and 15 in a four-week schedule.

Conflicts of Interest

There are no conflicts of interest to disclose.

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