Randomized Phase II Trial of Paclitaxel Plus Carboplatin Therapy Versus Irinotecan Plus Cisplatin Therapy as First-Line Chemotherapy for Clear Cell Adenocarcinoma of the Ovary

A JGOG Study

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Introduction: Paclitaxel plus carboplatin (TC) is generally considered to be the "gold standard" regimen for treatment of epithelial ovarian carcinomas. Little data are available, however, on the use of this regimen in patients with clear cell adenocarcinoma of the ovary (CCC). Combination chemotherapy with irinotecan hydrochloride plus cisplatin has been reported to be effective for primary and recurrent or resistant CCC. We compared these 2 combinations in patients with CCC.

Methods: Patients (n = 99) with CCC were randomly assigned to receive either 180 mg/m^2 paclitaxel on day 1 plus AUC 6 mg/mL × minute carboplatin on day 1 every 21 days (TC arm) or 60 mg/m^2 irinotecan hydrochloride on days 1, 8, 15 plus 60 mg/m^2 cisplatin on day 1 every 28 days (CPT-P arm).

Results: Percentages of patients receiving the scheduled 6 cycles of chemotherapy in the TC and CPT-P arms were 70.8% and 72.0%, respectively. Although toxicity was well tolerated in both arms, the toxicity profile of each arm differed. Progression-free survival (PFS) showed no significant difference between the 2 treatment groups. Because there were more patients with large residual disease in the CPT-P arm, we performed a subset analysis by removing those patients, and then compared the PFS with that of patients without residual disease or with residual disease less than 2 cm. The PFS tended to be longer in the CPT-P group, although the difference was not statistically significant.

Conclusions: A phase III randomized trial is required to elucidate the effectiveness of CPT-P combination chemotherapy for CCC.

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Clear cell adenocarcinoma of the ovary (CCC) has been recognized as a distinct histological entity under the World Health Organization classification of ovarian tumors since 1973. Clear cell adenocarcinoma of the ovary accounts for between 3.7% and 12.1% of all epithelial carcinomas, and its incidence is much higher in Japan than in the United States or Europe.[1–3] Many studies have shown that conventional platinum-based chemotherapy regimens such as cyclophosphamide plus cisplatin, cyclophosphamide plus cisplatin plus doxorubicin, and cyclophosphamide plus carboplatin yielded a poorer prognosis in patients with CCC than in patients with serous cystadenocarcinoma of the ovary.[1,4,5]

Paclitaxel plus carboplatin (TC) is generally considered to be the "gold standard" regimen for treatment of epithelial ovarian carcinomas according to the results of several randomized phase III trials.[6–8] This regimen has been used widely for all histological subtypes of epithelial ovarian carcinoma, including CCC. However, only 2% to 5% of the patients enrolled in these randomized trials had CCC.[6–8] Several retrospective and prospective studies have recently reported that response in measurable CCC cases treated with TC was relatively low, ranging from 22% to 56%.[9–11] The survival benefit of the TC regimen compared with conventional platinum-based regimens is also controversial; 1 study showed superior survival benefit,[12] whereas another implied no survival benefit in either early or advanced cases.[13]

Combination chemotherapy with irinotecan hydrochloride plus cisplatin (CPT-P) has been used clinically for patients with several types of human cancer. One large clinical trial, in particular, revealed that CPT-P showed significant activity for extensive small-cell lung cancer.[14] Moreover, it was reported that CPT-P therapy was effective for primary advanced and recurrent or resistant CCC.[2,3,15–17] One retrospective study also reported that progression-free survival (PFS) in CCC cases treated with CPT-P therapy was significantly better than in those treated with paclitaxel plus platinum.[17]

The Japanese Gynecologic Oncology Group (JGOG) conducted a randomized phase II study to compare CPT-P with TC in patients with CCC (JGOG3014).

MATERIALS AND METHODS

This phase II, centrally randomized, multicenter, open-label comparative trial included 37 independent investigative sites in Japan. A total of 99 patients were randomly assigned to either the TC or CPT-P treatment arm between January 2002 and July 2005. The study was performed in accordance with the principles of good clinical practice, applicable laws, and regulations, and the Declaration of Helsinki. Informed consent was obtained from all patients entered into the trial. Each institution obtained institutional review board approval of the protocol before study initiation.

Patient Eligibility

To be included in the study, patients had to have undergone surgery for ovarian carcinoma and the appropriate tissue be available for histological evaluation. Patients had to have histologically confirmed CCC and be at International Federation of Gynecology and Obstetrics (FIGO) stage Ic to IV, with or without residual disease after initial surgery. Stage Ic with capsule rupture during surgery was excluded. In cases where other histological cell types were concurrently present, clear cell histology had to be dominant. Histological diagnosis was confirmed by central pathological review after registration. Patients had to enter the study within 4 weeks of undergoing surgery, with no previous chemotherapy or radiation for ovarian cancer. Other eligibility criteria included written informed consent; an Eastern Cooperative Oncology Group performance status (PS) score of 0 or 1; aged 15 to 75 years; and adequate organ function. *Adequate organ function* (adequate function of the bone marrow, liver, and kidney) was defined as being indicated by a leukocyte count of at least 3000/μL, an absolute neutrophil count of at least 1500/μL, a hemoglobin level of at least 9.5 g/dL, a platelet count of at least 100,000/μL, a serum bilirubin level of less than 1.5 mg/dL, aspartate aminotransferase and alanine aminotransferase values of no more than twice the upper level of normal for the institution involved, and a creatinine clearance of at least 60 mL/min or serum creatinine level of less than 1.3 mg/dL when creatinine clearance was not applicable.

Exclusion criteria were as follows: serious concurrent disease of the liver, kidney, or heart; bone marrow suppression; systemic infection; diarrhea greater than National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade 1 (grade 2, 3, or 4); intestinal palsy; ileus; symptomatic brain metastasis; massive pleural or peritoneal effusion; a history of severe drug allergy; and pregnancy or breast-feeding. Patients with a history of other invasive malignancies, with the exception of nonmelanoma skin cancer and localized breast cancer, were excluded if there was any evidence of other malignancy being present within the previous 5 years.

Treatment Plan

Patients ware randomly assigned to either the paclitaxel plus carboplatin arm (TC) or the irinotecan hydrochloride

plus cisplatin arm (CPT-P) by the minimization method of balancing groups according to FIGO stage (I or II vs III or IV) and residual tumor size (<1 cm vs ≥1 cm). Randomization was performed at the JGOG data center according to the order in which information on enrollment was received by fax. Women in the TC arm received paclitaxel (180 mg/m^2) intravenously for 3 hours, followed by carboplatin (AUC 6 mg/mL × minute) intravenously for 1 to 2 hours on day 1 every 3 weeks for a total of 6 courses. The carboplatin dose was calculated using the Calvert formula; carboplatin dose (in milligrams) = AUC × (GFR + 25). The glomerular filtration rate was estimated using the Jelliffe formula. Patients assigned to the TC arm were premedicated with dexamethasone (20 mg intravenously 12–14 and 6–7 hours or 30 minutes before the start of paclitaxel infusion). Both diphenhydramine (50 mg orally) and ranitidine (50 mg intravenously) or famotidine (20 mg intravenously) were also administered 30 minutes before paclitaxel infusion. Patients in the CPT-P arm received irinotecan hydrochloride (60 mg/m^2) intravenously for 90 minutes on days 1, 8, and 15 and cisplatin (60 mg/m^2) intravenously for 1–2 hours on completion of irinotecan hydrochloride infusion on day 1 every 4 weeks for a total of 6 courses. Patients assigned to the CPT-P arm received prechemotherapy and postchemotherapy hydration to avoid cisplatin-induced nephrotoxicity. In all patients, antiemetic prophylaxis consisted of serotonin type 3 receptor antagonists and corticoids.

Dose Modifications and Modifications in Treatment Schedule

Adverse events were graded according to the NCI-CTCAE, version 2.0. Treatment modifications included skip, cycle delay, and dose reduction. Administration of irinotecan hydrochloride was skipped on day 8 or 15 if absolute neutrophil count was less than 1500/μL, if platelet count was less than 100,000/μL, or if there was grade 2 or higher diarrhea. Treatment in successive cycles was delayed if leukocyte count was less than 3000/μL, if absolute neutrophil count was less than 1500/μL, if platelet count was less than 100,000/μL, if creatinine clearance was less than 60 mL/min or serum creatinine level was 1.3 mg/dL and greater when creatinine clearance was not applicable, or if there was grade 2 or higher diarrhea. Otherwise, treatment in successive cycles could be recommenced with dose reductions in the TC arm (paclitaxel at 150 mg/m^2 and carboplatin AUC 5 mg/mL × minute) and CPT-P arm (irinotecan hydrochloride at 50 mg/m^2 and cisplatin at 50 mg/m^2) when the successive cycle was delayed for more than 2 weeks after the previous cycle if the patient had a leukocyte count of at least 2000/μL, an absolute neutrophil count of at least 1000/μL, a platelet count of at least 75,000/μL, a creatinine clearance of at least 50 mL/min or serum creatinine level less than 1.3 mg/dL when creatinine clearance was not applicable, and grade 1 or no diarrhea. Treatment was terminated if the next cycle was delayed for more than 2 weeks, if the leukocyte count was less than 2000/μL, if the absolute neutrophil count was less than 1000/μL, if the platelet count was less than 75,000/μL, if the creatinine clearance was less than 50 mL/min or serum creatinine level was 1.3 mg/dL and greater when creatinine clearance was not applicable, or if there was grade 2 or higher diarrhea.

Evaluations

All patients underwent weekly evaluations that included an assessment of symptoms, a physical examination, a complete blood cell count, and blood chemistry studies (including measurements of serum bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, and serum creatinine). Creatinine clearance was measured before each treatment cycle.

In patients with measurable disease, tumor response was evaluated according to World Health Organization criteria (1979) and assessed by computed tomography or magnetic resonance imaging, which was performed every 2 cycles. A *complete response* (CR) was defined as the disappearance of all clinical and radiological evidence of tumor for at least 4 weeks; a *partial response* (PR) was defined as a decrease of 50% or more in the sum of the products of the longest perpendicular diameters of all measurable lesions for at least 4 weeks; *progressive disease* (PD) was defined as an increase of more than 25% in the sum of the products of the perpendicular diameters of all measurable lesions or the appearance of new lesions. All other circumstances were considered to indicate *no change* (NC).

Statistical Analysis

The primary end point in this study was PFS, and the secondary end points were overall survival (OS), response rates, and adverse events. This was the first prospective study of CCC patients, and no retrospective analyses focusing on PFS or OS in a large number of such patients treated with TC or CPT-P therapy had been published before January 2002. Therefore, it was impossible to calculate the accrual sample size based on statistical method. Furthermore, response rate could not be established as the primary end point because usually most CCC patients have no measurable disease as assessed by computed tomography or magnetic resonance imaging after primary surgery. Therefore, we planned a phase II study to include 120 patients, with 60 patients in each group and PFS as the primary end point. The planned duration of accrual was 3.5 years, and the planned follow-up was 5 years. Only eligible cases with histologically confirmed CCC by central pathological review were included in the analysis of PFS, OS, and response rates. Only eligible women receiving at least 1 course of treatment were included in the assessment of adverse events.

All comparisons of patient characteristics, prognostic variables, response rates, and rates of adverse effects were performed with Fisher exact test, except for age, for which the Wilcoxon rank sum test was used. The PFS and OS were measured from the date of initial surgery. *Duration of PFS* was defined as minimum amount of time until clinical progression, death, or date of last contact. Duration of OS was measured up to the date of death or, for patients still alive, the date of last contact. Survival curves were calculated by the Kaplan-Meier method and compared with by the log-rank test. The multiple Cox regression model was used to explore the impact of specific prognostic factors on PFS.

RESULTS

Patient Characteristics

Initially, the sample size was planned to include 120 patients. However, this accrual target proved impossible to meet. Therefore, finally, we analyzed 99 patients enrolled during the 42-month planned accrual period (January 2002–July 2005). Fifty patients were assigned to the TC arm and 49 patients to the CPT-P arm. One patient in the CPT-P arm refused to allow submission of her case report form to the data center. Therefore, the full analysis sets (FASs) for the CPT-P and TC arms were 48 and 50 patients, respectively. After central pathology review, 5 cases were excluded because of wrong cell type, which included clear cell borderline tumor with microinvasion, serous borderline tumor with micropapillary pattern, transitional cell carcinoma, malignant mixed epithelial tumor (endometrioid adenocarcinoma, 75%; clear cell carcinoma, 25%), and endometrioid adenocarcinoma. One of them was in the CPT-P arm and 4 were in the TC arm. Therefore, an analysis for per protocol set (PPS) was performed for 47 patients in the CPT-P arm and 46 patients in the TC arm. The median follow-up time for this trial was 31.6 months.

Patient characteristics in FAS and PPS are shown in Table 1. Comparison of characteristics in FAS and PPS revealed a similar distribution in both treatment arms in terms of residual tumor less than or greater or equal to 1 cm, stages Ic-II or III-IV, age, and with or without complications. Nevertheless, PS was slightly poorer in the CPT-P arm, with 7 patients of 48 in FAS and 47 in PPS with PS 1, but only 1 patient with PS 1 in the TC arm (FAS, F = 0.044; PPS, F = 0.043). Although the number of patients in FAS and PPS was well balanced in terms of size of residual tumor greater or equal to 1 cm or less than 1 cm, there were more patients with residual tumor greater or equal to 2 cm in the CPT-P arm (11 patients compared with 4 patients in the TC

TABLE 1. Patient characteristics

	FAS (n = 98)			PPS (n = 93)		
Characteristic	**CPT-P (n = 48)**	**TC (n = 50)**	**Test**	**CPT-P (n = 47)**	**TC (n = 46)**	**Test**
Age, yr			W = 0.551			W = 0.900
Mean	54	58		54	54	
Range	31–70	33–75		31–70	33–75	
PS			F = 0.044			F = 0.043
0	40	48		39	45	
1	7	1		7	1	
Unknown	1	1		1	0	
Complications			F = 0.891			F = 1.000
Yes	8	7		8	7	
No	40	42		39	39	
Unknown	0	1		0	0	
FIGO stage			F = 0.833			F = 0.830
Ic–II	30	32		29	30	
III–IV	18	18		18	16	
Ic	25	22		24	22	
IIc	5	10		5	8	
IIIa	1	0		1	0	
IIIb	0	3		0	3	
IIIc	14	12		14	10	
IV	3	3		3	3	
Residual tumor			F = 0.321			F = 0.189
<1 cm	36	42		35	40	
≥1 cm	12	8		12	6	
Microscopic	30	34		29	32	
0 cm < < 1 cm	6	8		6	8	
1 cm ≤ < 2 cm	1	4		1	4	
≥ 2 cm	11	4		11	2	

F, Fisher exact test; W, Wilcoxon rank sum test.

TABLE 2. No. cycles by treatment

	CPT-P (n = 48)		TC (n = 50)	
Cycle	No. Patients	%	No. Patients	%
0	0	0	0	0
1	3	6.2	1	2.0
2	4	8.3	4	8.0
3	3	6.2	5	10.0
4	3	6.2	3	6.0
5	3	1.2	1	2.0
6	34	70.8	36	72.0

arm in FAS and 11 patients compared with 2 patients in the TC arm in PPS).

Treatment Administration

No significant differences were observed between the 2 groups in delivery of treatment (Table 2). The populations of patients in the TC and CPT-P arms in FAS who received the planned 6 cycles of chemotherapy were 70.8% (95% confidence interval [CI], 55.9–83.0) and 72.0% (95% CI, 57.5–83.8), respectively.

Adverse Events

Adverse events were graded according to the NCI-CTCAE, version 2.0. Major adverse events are shown in Table 3. None of the patients developed neutropenic fever. Incidence of grade 3 or worse leukopenia, neutropenia, anemia, and thrombocytopenia developed in 60.0%, 86.0%, 32.0%, and 24.0%, respectively, of the patients in the TC arm in FAS, and in 50.0%, 72.9%, 45.8%, and 4.2%, respectively, of the patients in the CPT-P arm in FAS. Grade 3 or worse thrombocytopenia occurred more frequently in the TC arm than in the CPT-P arm (odds ratio, 0.14; 95% CI, 0.03–0.65; $P = 0.0077$).

Grade 3 or worse nausea, vomiting, and diarrhea occurred in 16.0%, 8.0%, and 2.0%, respectively, of the patients in the TC arm in FAS, and in 31.3%, 16.7%, and 10.4%, respectively, of the patients in the CPT-P arm in FAS. Although

TABLE 3. Major adverse events

		No. Patients					% of Patients (95%CI)	Odds Ratio (95%CI)
		Grade						
Adverse Event	Treatment Arm (n)	1	2	3	4	3 or 4	3 or 4	3 or 4
Hematological								
Leukopenia	CPT-P (48)	5	19	22	2	24	50.0 (35.2–64.8)	0.67
	TC (50)	3	16	29	1	30	60.0 (45.2–73.6)	(0.30–1.48)
Neutropenia	CPT-P (48)	2	7	23	12	35	72.9 (58.2–84.7)	0.44
	TC (50)	2	3	12	31	43	86.0 (73.3–94.2)	(0.16–1.22)
Thrombocytopenia	CPT-P (48)	16	4	2	0	2	4.2 (0.5–14.3)	**0.14***
	TC (50)	26	5	9	3	12	24.0 (13.1–38.2)	**(0.03–0.65)***
Anemia	CPT-P (48)	4	15	19	3	22	45.8 (31.4–60.8)	1.80
	TC (50)	3	22	12	4	16	32.0 (19.5–46.7)	(0.79–4.09)
Nonhematological								
Nausea	CPT-P (48)	12	19	14	1	15	31.3 (18.7–46.3)	2.39
	TC (50)	20	17	8	0	8	16.0 (7.2–29.1)	(0.90–6.31)
Vomiting	CPT-P (48)	13	16	7	1	8	16.7 (7.5–30.2)	2.3
	TC (50)	14	10	4	0	4	8.0 (2.2–19.2)	(0.64–8.21)
Diarrhea	CPT-P (48)	12	10	5	0	5	10.4 (3.5–22.7)	5.7
	TC (50)	6	2	1	0	1	2.0 (0.1–10.6)	(0.64–50.69)
Alopecia	CPT-P (48)	25	17	—	—	—	—	
	TC (50)	11	38	—	—	—	—	
Peripheral motor neuropathy†	CPT-P (48)	6	5	0	0	5	10.4 (3.5–22.7)	0.53
	TC (50)	12	8	1	0	9	18.0 (8.6–31.4)	(0.16–1.71)
Peripheral sensory neuropathy†	CPT-P (48)	9	3	0	0	3	6.3 (1.3–17.2)	**0.19***
	TC (50)	29	12	1	0	13	26.0 (14.6–40.3)	**(0.05–0.72)***

Adverse events were graded according to NCI-CTCAE, version 2.0.
*Statistically significant difference between treatment arms.
†Incidence of neurotoxicities was calculated for grades 2/3/4.

the difference was not statistically significant, grade 3 or worse gastrointestinal toxicities were more frequent in the CPT-P arm. Grade 2 or worse peripheral sensory and motor neuropathy occurred in 26.0% and 18.0%, respectively, of the patients in the TC arm in FAS, and in 6.3% and 10.4%, respectively, of the patients in the CPT-P arm in FAS. Grade 2 or worse peripheral sensory neuropathy occurred more frequently in the TC arm (odds ratio, 0.19; 95% CI, 0.05–0.72; $P = 0.0015$).

Efficacy

Clinical response was assessed in the 13 patients in the PPS with clinically measurable disease. Clinical response results are listed in Table 4. There were 2 CR, 2 NC, and 4 PD among the 8 assembled patients in the CPT-P group, and overall response rate was 25% (95% CI, 3.2%–65.1%) in the CPT-P group. There were 1 CR, 1 PR, and 3 PD among the 5 assembled patients in the TC group, and overall response rate was 40% (95% CI, 5.3%–85.3%). No significant difference was observed in overall response rate between the 2 treatment groups.

Survival results are shown in Figure 1. The PFS was compared for all patients in PPS and FAS. No significant difference was observed between the 2 treatment groups (PPS, $P = 0.9089$ by the log-rank test, Fig. 1A; FAS, $P = 0.9035$ by the log-rank test, data not shown), and the relative risk of disease progression in the TC group as compared with that in the CPT-P group was 1.034 (95% CI, 0.583–1.835) in PPS and 0.964 (95% CI, 0.544–1.710) in FAS. Because there were more patients in the CPT-P arm (11 patients in PPS and FAS) than in the TC arm (2 patients in PPS; 4 patients in FAS) with larger residual disease greater than or equal to 2 cm, we performed a subset analysis by removing those patients and then compared the PFS with patients without residual disease or with residual disease less than 2 cm. The PFS tended to be longer in the CPT-P group, although the difference was not statistically significant (PPS, $P = 0.2702$ by the log-rank test, Fig. 1B; FAS, $P = 0.3176$ by the log-rank test, data not shown), and the relative risk of disease progression in the TC group as compared with that in the CPT-P group was 1.465 (95% CI, 0.757–2.836) in PPS and 1.414 (95% CI, 0.730–2.739) in FAS.

TABLE 4. Objective tumor response

	CPT-P (n = 8)		TC (n = 5)	
	No. Patients	%	No. Patients	%
CR	2	25	1	20
PR	0	0	1	20
Overall response:				
CR + PR	2	25	2	40
95% CI		3.2–65.1		5.3–85.3
NC	2	25	0	0
PD	4	50	3	60

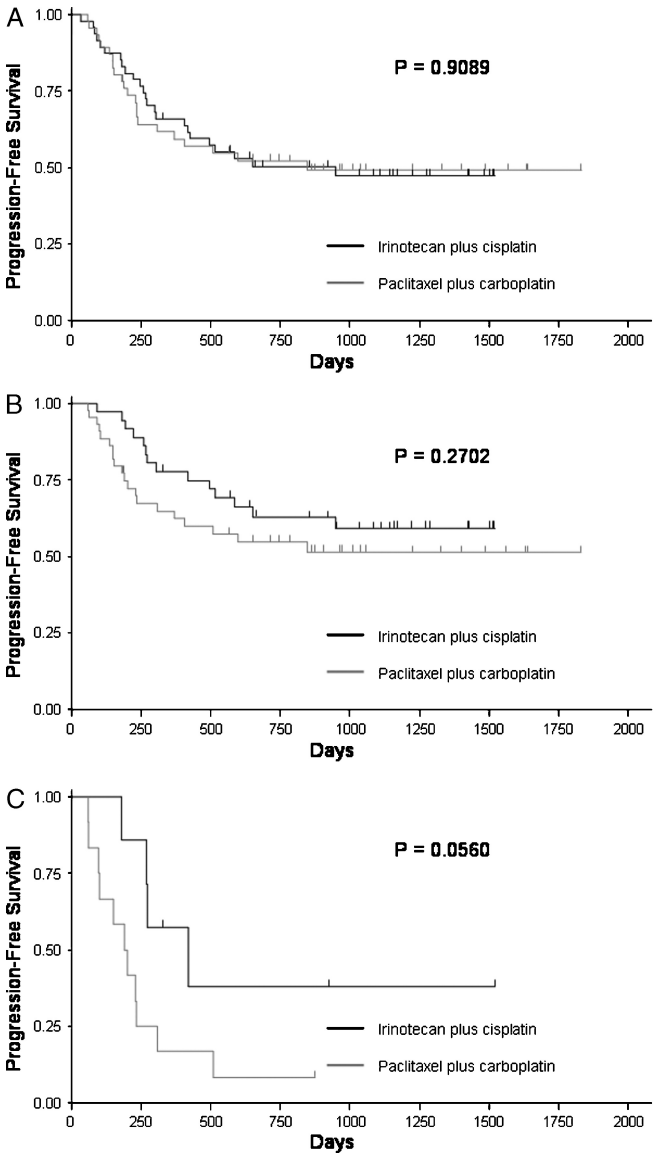

FIGURE 1. Progression-free survival by treatment group. A, Progression-free survival in all patients in PPS by treatment group. B, Progression-free survival in patients without residual disease or with residual disease of less than 2 cm in PPS by treatment group. C, Progression-free survival in patients with residual disease of less than 2 cm in PPS by treatment group.

Furthermore, we compared PFS in patients with residual disease less than 2 cm. There was a strong tendency that PFS was longer in the CPT-P group, although the difference was not statistically significant (PPS and FAS, $P = 0.056$ by the log-rank test, Fig. 1C), and the relative risk of disease progression in the TC group was significantly higher than that in the CPT-P group (2.945; 95% CI, 1.052–8.246) in PPS and FAS.

We also compared PFS in patients with no residual disease. No significant difference was observed between the

2 treatment groups (PPS, $P = 0.8479$ by the log-rank test, data not shown; FAS, $P = 0.7774$ by the log-rank test, data not shown).

A comparison of OS in all patients in PPS and FAS revealed no significant difference between the 2 treatment groups (PPS, $P = 0.2834$ by the log-rank test, data not shown; FAS, $P = 0.2217$ by the log-rank test, data not shown).

DISCUSSION

The CCC has been suggested to lack sensitivity compared with conventional platinum-based chemotherapy.[1,4,5] Paclitaxel plus carboplatin is generally considered to be the gold standard regimen for epithelial ovarian carcinomas. However, the survival benefit of TC compared with conventional platinum-based regimens in CCC patients is controversial.[12,13] On the other hand, it was reported that CPT-P therapy was effective for primary advanced and recurrent or resistant CCC.[2,3,15–17] We conducted a randomized phase II study, JGOG3014, to compare the efficacy and toxicity of CPT-P against TC in patients with CCC.

Although the toxicities of CPT-P and TC were well tolerated, the toxicity profile of each treatment differed. Paclitaxel plus carboplatin produced more thrombocytopenia and peripheral sensory neuropathy. Although the difference was not statistically significant, CPT-P produced more gastrointestinal toxicities. The toxicity results for the TC and CPT-P regimens were similar to those obtained in several phase II and phase III studies for advanced ovarian cancer.[8,18,19]

One retrospective study reported that PFS in patients with optimally resected stages II to IV CCC treated with CPT-P therapy was significantly better than that with paclitaxel plus platinum; that no significant difference was observed in PFS in patients with stage I CCC and patients with suboptimally resected CCC between the 2 treatment groups; and that multiple regression survival analysis revealed that CPT-P regimen and residual tumor diameter were both independent prognostic factors in stages II to IV CCC.[17] The authors suggested that CPT-P had a potential therapeutic benefit for advanced CCC, especially in cases with optimal debulking surgery.[17] Another retrospective study also reported that the estimated 2- and 5-year PFS rates for 35 patients with stage Ic (ascites/malignant washing) to IV CCC treated with CPT-P were 55% and 55%, respectively, and those for 82 patients treated with TC were 48% and 40%, respectively ($P = 0.31$).[20] The authors suggested that CPT-P showed a potential therapeutic effect of at least no less than that of TC therapy.[20] In our study, PFS showed no significant difference between the 2 treatment groups. Nevertheless, in a subset analysis, PFS for patients without residual disease or with residual disease less than 2 cm tended to be longer in the CPT-P group, although the difference was not statistically significant ($P = 0.2702$). This is probably caused by the small sample size. Moreover, in a small subset analysis for patients with residual disease less than 2 cm, the relative risk of disease progression in the TC group was significantly higher than that in the CPT-P group (2.945; 95% CI, 1.052–8.246). These results suggest that CPT-P has a potential therapeutic benefit greater than that of TC therapy for CCC. A phase III randomized trial is required to elucidate the efficacy of CPT-P combination chemotherapy in CCC.

Taken together with those from earlier reports, our data suggest that CPT-P is a candidate first-line chemotherapy regimen for CCC. However, TC is still generally considered to be the standard first-line chemotherapy for ovarian cancer. At present, the JGOG and the Gynecologic Cancer Intergroup is performing an international cooperative randomized phase III trial of TC therapy versus CPT-P therapy as a first-line chemotherapy for CCC (GCIG/JGOG 3017 ovarian trial), and the results are eagerly awaited.

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