VOLUME 34 · NUMBER 24 · AUGUST 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Trial of Irinotecan Plus Cisplatin Compared With Paclitaxel Plus Carboplatin As First-Line Chemotherapy for Ovarian Clear Cell Carcinoma: JGOG3017/GCIG Trial

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Published online ahead of print at www.jco.org on July 11, 2016.

Written on behalf of the JGOG3017 investigators.

Supported by the Japanese Gynecologic Oncology Group.

Presented at the 50th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 30-June 3, 2014.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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0732-183X/16/3424w-2881w/$20.00

DOI: 10.1200/JCO.2016.66.9010

ABSTRACT

Purpose

Clear cell carcinoma (CCC) is a rare histologic subtype that demonstrates poor outcomes in epithelial ovarian cancer. The Japanese Gynecologic Oncology Group conducted the first randomized phase III, CCC-specific clinical trial that compared irinotecan and cisplatin (CPT-P) with paclitaxel plus carboplatin (TC) in patients with CCC.

Patients and Methods

Six hundred sixty-seven patients with stage I to IV CCC of the ovary were randomly assigned to receive irinotecan 60 mg/m^2 on days 1, 8, and 15 plus cisplatin 60 mg/m^2 on day 1 (CPT-P group) every 4 weeks for six cycles or paclitaxel 175 mg/m^2 plus carboplatin area under the curve 6.0 mg/mL/min on day 1 every 3 weeks for six cycles (TC group). The primary end point was progression-free survival. Secondary end points were overall survival, overall response rate, and adverse events.

Results

Six hundred nineteen patients were clinically and pathologically eligible for evaluation. With a median follow-up of 44.3 months, 2-year progression-free survival rates were 73.0% in the CPT-P group and 77.6% in TC group (hazard ratio, 1.17; 95% CI, 0.87 to 1.58; $P = .85$). Two-year overall survival rates were 85.5% with CPT-P and 87.4% with TC (hazard ratio, 1.13; 95% CI, 0.80 to 1.61; one-sided $P = .76$). Grade 3/4 anorexia, diarrhea, nausea, vomiting, and febrile neutropenia occurred more frequently with CPT-P, whereas grade 3/4 leukopenia, neutropenia, thrombocytopenia, peripheral sensory neuropathy, and joint pain occurred more frequently with TC.

Conclusion

No significant survival benefit was found for CPT-P. Both regimens were well tolerated, but the toxicity profiles differed significantly. Treatment with existing anticancer agents has limitations to improving the prognosis of CCC.

J Clin Oncol 34:2881-2887. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Ovarian cancer is the seventh most common cancer diagnosis among women worldwide.[1] Approximately 90% of ovarian cancers are epithelial carcinomas, which are the most lethal type of gynecologic malignancy.[2] High-grade serous carcinoma accounts for approximately 70% of epithelial ovarian cancers (EOCs), whereas clear cell carcinoma (CCC) is considered to be a rare tumor. The prevalence of CCC is largely region and ethnicity specific; CCC accounts for approximately 10% of EOCs in Europe and the United States, whereas it is more prevalent in Asia, particularly in the Japanese population where it accounts for 24% of all EOCs.[3-6] CCC is less sensitive to platinum-based chemotherapy, and the median survival time of stage III/IV CCC is significantly lower than that of high-grade serous carcinoma.[5-10] Over the past half century, EOC has been investigated as a single disease in clinical studies, and paclitaxel plus carboplatin (TC) has been recommended as the global standard for EOC.[11-14] Only 2% to 5% of all patients

enrolled in large randomized controlled trials of EOC have CCC.[6,10,15] Consequently, these results have not provided a scientific rationale for recommending TC as the standard therapy for CCC of the ovary.

An in vitro study suggested that irinotecan (CPT-11) may be an effective agent to treat CCC.[16] Numerous case reports and small phase II studies in Japan have supported the effectiveness of CPT-11 plus cisplatin (CPT-P) for CCC.[17-22] The Japanese Gynecologic Oncology Group (JGOG) 3014 study,[22] which was the first randomized phase II study to compare TC versus CPT-P for CCC of the ovary, showed that toxicity was well tolerated in both arms, but the toxicity profile of each arm differed. Thrombocytopenia and peripheral sensory neuropathy were more frequently observed in the TC arm, whereas gastrointestinal toxicities, such as nausea, vomiting, and diarrhea, were more frequently observed in the CPT-P arm. In this study, the relative risk of disease progression was not statistically different between the groups. Because more patients with large residual disease were in the CPT-P arm, a subset analysis was performed by removing those patients and comparing progression-free survival (PFS) with that of patients without residual disease or with residual disease $<$ 2 cm. Although the difference was not statistically significant, the PFS tended to be longer in the CPT-P group in both subsets, which led to the present appropriately powered phase III trial. Since 2000, the evaluation of novel and potentially more effective regimens for CCC by conducting histotype-specific trials has been important. We conducted the first randomized phase III, CCC-specific clinical trial of CPT-P compared with TC in treating patients with CCC of the ovary. There is now a global consensus on the necessity of defining treatment strategy by histologic subtype for which we propose international central pathologic review as a prerequisite.

PATIENTS AND METHODS

Study Design and Conduct

In the international, intergroup, multi-institutional, randomized phase III study, primary coordination was provided by the JGOG (lead group) in collaboration with the Gynecologic Cancer Intergroup (GCIG; JGOG3017/GCIG Trial). Cooperative groups other than JGOG were the Korean Gynecologic Oncology Group, UK institutions participating under the auspices of the National Cancer Research Institute through the Scottish Gynecologic Cancer Trials Group, Multicenter Italian Trials in Ovarian Cancer, and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens, and all groups needed to refer to their group-specific appendix within the study protocol for their registration/randomization procedure.

The primary objective was to compare the efficacy and safety of the standard group of TC and experimental group of CPT-P in CCC of the ovary. The primary end point was PFS, and secondary end points were overall survival (OS); overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0; and adverse events (AEs) with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Patients

Patients were recruited at multiple international institutions from September 2006 to February 2011. Eligible patients had a histologic diagnosis of stage I to IV CCC. All patients must have had comprehensive staging surgery for ovarian carcinoma with appropriate tissue available for histologic evaluation. They were also required to be enrolled in the trial within 6 weeks of surgery. In the case of concurrent presence of other histologic cell types, clear cell histology was required to be the dominant type ($>$ 50%). The histologic diagnosis was confirmed by an international central pathology review (CPR) after registration. Patients were required to be age 18 years or older and have an Eastern Cooperative Oncology Group performance status of 0 or 1. Adequate hematologic, renal, and hepatic function were required to include an absolute neutrophil count of $\geq$ 1,500/μL, platelet count of $\geq$ 100,000/μL, bilirubin of $\leq$ 1.5 $\times$ institutional upper limit of normal (ULN), AST and alkaline phosphatase level $\leq$ 2.5 $\times$ institutional ULN, and serum creatinine $\leq$ 1.5 $\times$ institutional ULN. Patients who had tumors of low malignant potential, with synchronous primary endometrial cancer, or a history of primary endometrial cancer were not eligible. Patients who had received radiotherapy or chemotherapy were not eligible. Patients with diarrhea and/or neuropathy (sensory and motor) greater than Common Terminology Criteria for Adverse Events (version 3.0) grade 1 were not eligible. Participating institutional review boards approved the protocol, and all patients provided written informed consent. The protocol was coordinated by the JGOG (protocol number 3017).

Random Assignment and Treatment

All participating institutions or the coordinating center of the study group were required to complete the GCIG/JGOG3017 Institution Registration Form to provide an institutional review board approval certificate for this trial as well as institutional contact information. Eligible patients were randomly assigned 1:1 to one of two treatment regimens in equal proportions by the Kitasato University Research Center for Clinical Pharmacology Clinical Trial Coordinating Center randomization system. Primarily, all patients were required to be registered through a Web-based patient registration system. They were stratified according to region (Japan or not Japan), stage (IA to IB, IC, or II to IV), and size of residual disease (complete, optimal [$<$ 1 cm], or suboptimal [$\geq$ 1 cm]). The investigator administered the assigned protocol treatment. Eligible patients were randomly assigned to receive CPT-11 60 mg/m^2 on days 1, 8, and 15 plus cisplatin 60 mg/m^2 on day 1 every 4 weeks for six cycles (CPT-P group) or paclitaxel 175 mg/m^2 plus area under the curve 6.0 mg/mL $\times$ minute carboplatin on day 1 every 3 weeks for six cycles (TC group) with the use of Pocock and Simon's minimization method. No further anticancer therapy was to be given after the completion of six cycles of the protocol therapy until progression was documented.

Outcome Measures

All AEs were documented in the patient's medical records and case report form. All AEs were followed until resolution or for at least 30 days (except for alopecia, fatigue, nausea, or constipation), whichever came first, until toxicity had resolved to baseline, or until the toxicity was considered to be irreversible.

Statistical Analysis

The primary objective of this study was to determine whether the CPT-P group was superior to the TC group in the treatment of patients with CCC of the ovary as assessed by PFS. On the basis of the results of previous studies,[17,22] we assumed that the 5-year PFS rates for TC and CPT-P would be 40% and 50%, respectively. With an accrual period of 4.25 years and total duration of 6.5 years, 652 patients (323 events) were originally required for a one-sided type I error of 0.05 and a power of 80% by log-rank test. After protocol modification with a prolonged accrual period and total duration of 4.75 and 6.75 years, respectively, 662 patients (318 events) were finally required.

All efficacy analyses were performed for all randomly assigned patients whose histologic diagnosis was confirmed as CCC by CPR. The same analyses were done in all randomly assigned patients on the basis of the intent-to-treat (ITT) principle. All safety analyses were performed in all patients who received at least one protocol treatment. The primary end point was PFS. PFS curves, 2-year PFS rates, and their 95% CIs were

estimated by using the Kaplan-Meier method and Greenwood formula. Nonparametric 95% CIs were calculated for the median PFSs, and the curves were compared between treatment groups on the basis of one-sided unstratified log-rank test with an overall significance level of 5%. Unstratified hazard ratios (HRs) that compared CPT-P with TC and their 95% CIs were calculated with the use of Cox regression models. The same analyses were performed for the OS. ORRs and their exact 95% CIs were estimated in each treatment group. ORRs were compared with the use of Fisher exact test; odds ratios and their 95% CIs also were estimated. Subgroup analyses were conducted according to all randomization factors and other prespecified demographic variables. One formal interim analysis was carried out at approximately 6 months after the last patients were enrolled. To maintain an overall significance level of 5%, an O'Brien-Fleming boundary was calculated with the use of the Lan-DeMets method. Additionally, conditional power methods were used to aid the independent data monitoring committee in reaching decisions about study continuation in terms of futility. At all times of interim analyses, the independent data monitoring committee recommended continuation of the study.

For safety data analysis, the number and percentage of patients for each AE were summarized for each treatment group. The numbers and percentages of patients for grade 3/4 AEs were also estimated.

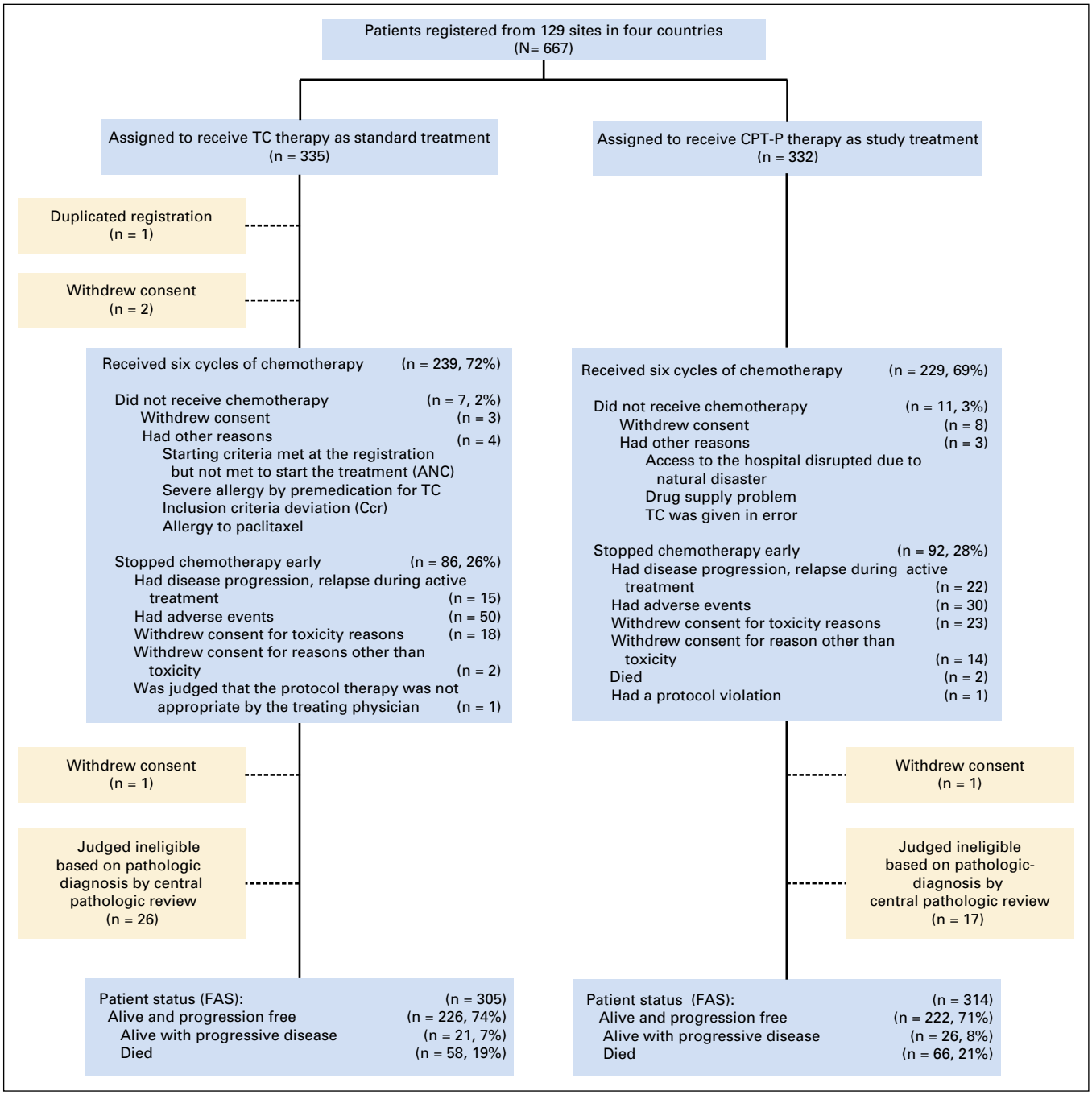

Fig 1. Enrollment, random assignment, and outcomes. ANC, absolute neutrophil count; Ccr, creatinine clearance; CPT-P, irinotecan plus cisplatin; FAS, full analysis set; TC, paclitaxel plus carboplatin.

RESULTS

Patients

Six hundred sixty-seven women were enrolled at 129 centers in Japan, Korea, France, and the United Kingdom, and 619 patients were clinically and pathologically eligible for evaluation (314 patients in the CPT-P group and 305 patients in the TC group). International CPR by 24 expert gynecologic pathologists from six countries was performed by using a Web-based system. Forty-three patients (6.4%) were ineligible due to non-CCC histology, four withdrew from the study, and one was duplicated. The final analysis was performed in 619 patients (Fig 1). The treatment groups were well balanced with respect to baseline characteristics (Table 1). Japanese women made up 93.5%. The median age was 53 years in both groups. For stage distribution, 411 (66.4%) patients were in stage I, with stage IC being the majority, and only 32 (5.2%) patients had measurable lesions postoperatively.

Study Treatment Received

In the safety population, approximately 72% of the patients in both groups received six cycles of chemotherapy (71.3% in the CPT-P group and 73.5% in the TC group). This rate was almost the same as the previous randomized phase II study, JGOG3014 (72.0% in the CPT-P group and 70.8% in the TC group).[22] A decrease in CPT-P and TC dosage was needed in 67 (20.9%) and 91 (28.0%) patients, respectively, and it was unnecessary for > 77% of patients to reduce platinum. Most patients who required the reduction were given it at level 1. After disease progression, 105 (17.0%) patients crossed over to another therapy (CPT-P to TC, 11.8%; TC to CPT-P, 22.0%).

Table 1. Baseline Characteristics of the Patients by Study Group

Variable	TC, No. (%)	CPT-P, No. (%)	Total, No. (%)
No. of patients	305	314	619
Age, years			
Median	53	53	53
Range	30-81	30-75	30-81
Race			
Japanese	281 (92.1)	298 (94.9)	579 (93.5)
Non-Japanese	24 (7.9)	16 (5.1)	40 (6.5)
ECOG performance status			
0	268 (87.9)	291 (92.7)	559 (90.3)
1	37 (12.1)	23 (7.3)	60 (9.7)
Stage			
IA to IB	49 (16.1)	47 (15)	96 (15.5)
IC	157 (51.5)	158 (50.3)	315 (50.9)
II to IV	99 (32.5)	109 (34.7)	208 (33.6)
Size of residual disease			
Complete	267 (87.5)	277 (88.2)	544 (87.9)
Optimal (≤ 1 cm)	19 (6.2)	17 (5.4)	36 (5.8)
Suboptimal (> 1 cm)	19 (6.2)	20 (6.4)	39 (6.3)

NOTE. No significant differences were found between groups in any of the characteristics. The sum of percentages may not equal 100% because of rounding.
Abbreviations: CPT-P, irinotecan plus cisplatin; ECOG, Eastern Cooperative Oncology Group; TC, paclitaxel plus carboplatin.

Efficacy

Progression-free survival. With 44.3 months median follow-up, disease progression or death occurred in 171 patients (92 in the CPT-P group and 79 in the TC group). Two-year PFS rates were 73.0% (95% CI, 67.7% to 77.5%) in CPT-P and 77.6% (95% CI, 72.4% to 81.9%) in TC. There was no significant difference in the two PFS curves (HR, 1.17; 95% CI, 0.87 to 1.58; one-sided $P = .85$; two-sided $P = .30$; Fig 2A). There was also no significant difference in ITT population (HR, 1.14; 95% CI, 0.85 to 1.52; one-sided $P = .81$; two-sided $P = .38$).

Overall survival. Death occurred in 124 patients (66 in the CPT-P group and 58 in the TC group). Two-year OS rates were 85.5% (95% CI, 81.1% to 89.0%) in CPT-P and 87.4% (95% CI, 83.1% to 90.7%) in TC. There was no significant difference in the two OS curves (HR, 1.13; 95% CI, 0.80 to 1.61; one-sided $P = .76$; two-sided $P = .49$; Fig 2B). There was also no significant difference in ITT population (HR, 1.06; 95% CI, 0.75 to 1.49; one-sided $P = .63$; two-sided $P = .75$).

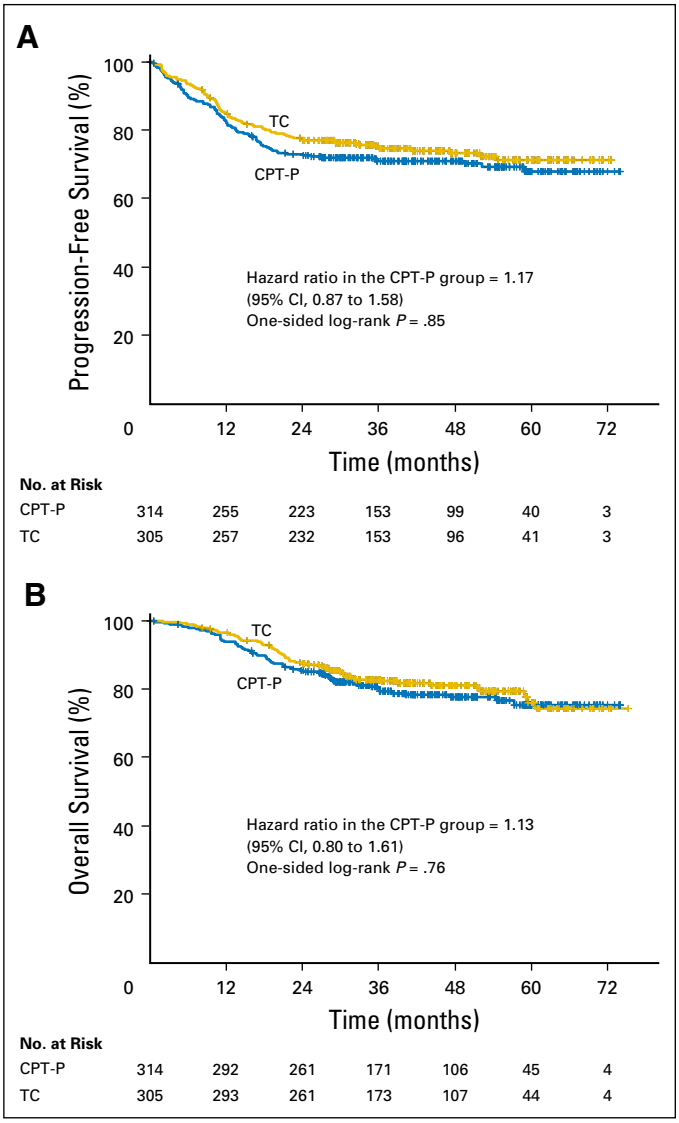

Fig 2. (A) Progression-free and (B) overall survival. CPT-P, irinotecan plus cisplatin; TC, paclitaxel plus carboplatin.

Table 2. Adverse Events, According to Study Group

Adverse Event	TC (n = 325), No. (%)		CPT-P (n = 321), No. (%)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Decreased hemoglobin	264 (81.2)	73 (22.5)	257 (80.1)	66 (20.6)
Decreased WBC*	308 (94.8)	207 (63.7)	288 (89.7)	140 (43.6)
Decreased ANC*	310 (95.4)	293 (90.2)	293 (91.3)	220 (68.5)
Decreased platelets*	228 (70.2)	46 (14.2)	109 (34.0)	9 (2.8)
Febrile neutropenia*	10 (3.1)	10 (3.1)	22 (6.9)	22 (6.9)
Anorexia*	199 (61.2)	5 (1.5)	251 (78.2)	23 (7.2)
Nausea*	214 (65.8)	3 (0.9)	281 (87.5)	32 (10.0)
Vomiting*	94 (28.9)	3 (0.9)	189 (58.9)	25 (7.8)
Diarrhea*	40 (12.3)	1 (0.3)	185 (57.6)	25 (7.8)
Rash/desquamation	57 (17.5)	3 (0.9)	24 (7.5)	1 (0.3)
Allergic reaction/hypersensitivity	32 (9.8)	2 (0.6)	8 (2.5)	0
Edema	24 (7.4)	1 (0.3)	35 (10.9)	0
Neuropathy/motor	74 (22.8)	9 (2.8)	15 (4.7)	2 (0.6)
Neuropathy/sensory*	258 (79.4)	24 (7.4)	59 (18.4)	3 (0.9)
Muscle pain	172 (52.9)	7 (2.2)	34 (10.6)	1 (0.3)
Joint pain*	175 (53.8)	10 (3.1)	20 (6.2)	0 (0.0)
Hair loss/alopecia	304 (93.5)	—	253 (78.8)	—

NOTE. Classified according to Common Terminology Criteria for Adverse Events (version 3.0).
Abbreviations: ANC, absolute neutrophil count; CPT-P, irinotecan plus cisplatin; TC, paclitaxel plus carboplatin.
*$P < .05$ for grade 3/4 adverse events with Fisher's exact test.

Best overall response. Only 32 (5.2%) patients had measurable disease (17 in the CPT-P group and 15 in the TC group). ORRs for the two treatment regimens were 29.4% (complete response, 17.6%; partial response, 11.8%) in CPT-P and 46.7% (complete response, 13.3%; partial response, 33.3%) in TC.

Adverse Events

No deaths related to treatment were reported. AEs are summarized in Table 2 as the number of patients who exhibited all grades. CPT-P seemed to be associated with an increase in grade 3/4 anorexia, diarrhea, nausea, vomiting, and febrile neutropenia ($P < .05$), whereas grade 3/4 leukopenia, neutropenia, thrombocytopenia, peripheral sensory neuropathy, and joint pain occurred more frequently in TC ($P < .05$). The incidence of anemia was similar in the two groups.

Subgroup Analyses

In PFS subgroup analysis, there was no significant difference between CPT-P and TC (Fig 3). In the stage I group, 2-year PFS rates were 89.1% in CPT-P and 89.7% in TC (HR, 0.97; 95% CI,

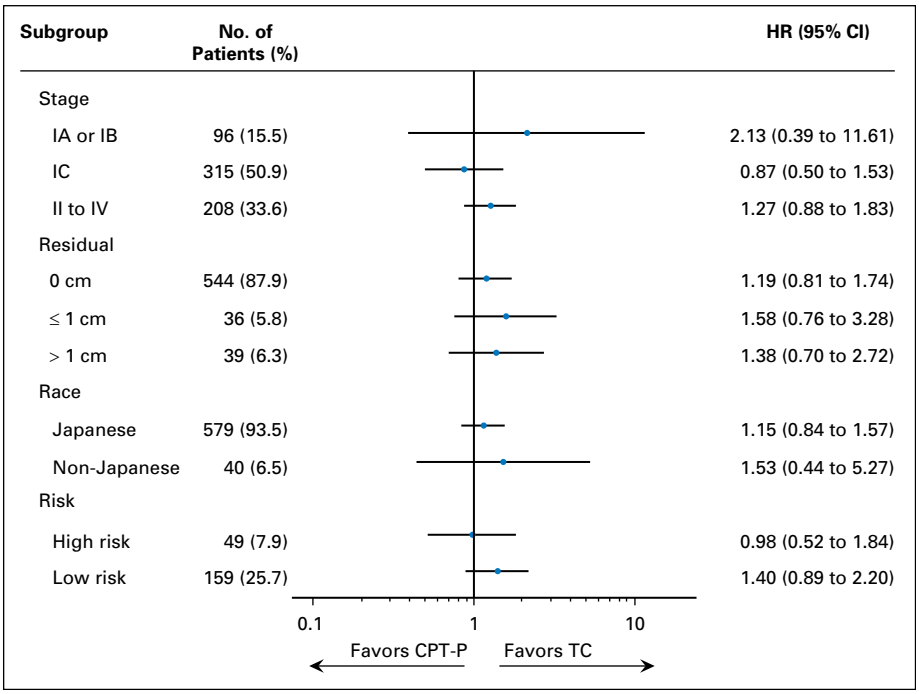

Fig 3. Subgroup analysis of progression-free survival. CPT-P, irinotecan plus cisplatin; HR, hazard ratio; TC, paclitaxel plus carboplatin.

0.57 to 1.64; two-sided $P = .90$). In stage II to IV disease, 2-year PFS rates were 42.6% in CPT-P and 52.5% in TC (HR, 1.27; 95% CI, 0.88 to 1.83; two-sided $P = 0.20$; Appendix Fig A1, online only). In the analyses of the stage II to IV groups stratified by the high-risk (suboptimal stage III + stage IV) and the low-risk (stage II + other stage III) groups, no significant differences in PFS and OS were found in either group (Appendix Fig A2, online only).

DISCUSSION

The primary end point PFS and the secondary end points OS and ORR in CPT-P were not superior to those in TC. Both regimens were well tolerated, but the toxicity profiles were different. Subgroup analyses by stratification factor at randomization were also conducted. No significant differences in PFS and OS were found in subgroup analyses by region, stage, and residual tumor size.

The timing of the scans during protocol therapy was more frequent in the TC arm than in the CPT-P arm because the study protocol–defined scan was to be done every three cycles, and the cycle lengths for TC was 3 weeks, whereas the cycle length for CPT-P was 4 weeks. The timing of the scans may have influenced the results against TC. However, after protocol therapy, patients were followed regularly at the same frequency in both arms, and the scan was obtained when disease progression was indicated. Because PFS curves were compared primarily on the basis of a one-sided log-rank test, we believe that the differences may have little influence on the survival results.

In this study, only 32 patients had measurable lesions, and ORR was 37.5%, which was similar to previous reports. On the basis of small-scale studies, the response rates to TC were varied but generally lower (18% to 56%).[6,10,15,23-25] CPT-P was considered to be effective in CCC according to retrospective and prospective studies in Japan[17-22]; however, its effect was not superior to that of TC in this phase III study. Although TC may still be the first-line therapy for CCC, the results of the current study simultaneously revealed that treatment with existing anticancer agents has limitations in improving the prognosis of CCC.

CCC frequently appears at early stages, especially stage IC.[4-6,9,26-28] In the current study, 66.4% of the patients had stage I and 33.6% had stage II to IV (stage III/IV, 23.3%) disease. The JGOG3014, the previous randomized phase II study, showed a tendency of PFS superiority of the CPT-P arm in a subset analysis of patients without residual disease or with residual disease < 2 cm. However, we could not identify the survival advantage of CPT-P in any subgroup analyses by region, stage, and size of the residual disease in the current phase III randomized trial.

The identification of driver mutations of CCC is a crucial first step toward personalizing treatment of CCC. Improvement in CCC prognosis has been shown by preliminary data wherein the combination of targeted agents, such as PI3K-Akt-mTOR pathway inhibitor[29-31] and antiangiogenic agents,[31-33] with CPT-11 and paclitaxel as well as anti–programmed cell death 1 antibody[34] was reported to be effective for metastatic renal cell carcinoma. Therefore, we emphasize that therapeutic regimens should consider such combinations and/or target drugs to improve the prognosis of CCC of the ovary.

The origin and pathogenesis of EOC has been poorly understood. Studies have shown that EOC is not a single disease but comprises a diverse group of tumors that can be classified based on distinctive morphologic and molecular genetics features.[2] This first histologic subtype–specific study of gynecologic oncology, which was conducted on the basis of the international CPR system is also the first international study (GCIG) led by Asian centers. Of note, 667 patients with CCC, a rare tumor worldwide, were enrolled for 4.3 years.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Final approval of manuscript: All authors

REFERENCES

1. Ferlay J, Shin HR, Bray F, et al: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127:2893-2917, 2010
2. Tavassori FA, Devilee P (eds): Surface epithelial stromal tumours: Tumours of the ovary and peritoneum, in World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Breast and Female Genital Organs. Lyon, France, IARC Press, 2003, pp 117-145
3. Annual report on Japanese ovarian cancer. Japanese gynecologic cancer committee. Acta Obstet Gynaecol Jpn 64:1029-1041, 2012
4. Chan JK, Teoh D, Hu JM, et al: Do clear cell ovarian carcinomas have poorer prognosis compared to other epithelial cell types? A study of 1411 clear cell ovarian cancers. Gynecol Oncol 109:370-376, 2008
5. Sugiyama T, Kamura T, Kigawa J, et al: Clinical characteristics of clear cell carcinoma of the ovary: A distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. Cancer 88:2584-2589, 2000
6. del Carmen MG, Birrer M, Schorge JO: Clear cell carcinoma of the ovary: A review of the literature. Gynecol Oncol 126:481-490, 2012
7. Kennedy AW, Biscotti CV, Hart WR, et al: Histologic correlates of progression-free interval and survival in ovarian clear cell adenocarcinoma. Gynecol Oncol 50:334-338, 1993
8. Goff BA, Sainz de la Cuesta R, Muntz HG, et al: Clear cell carcinoma of the ovary: A distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy in stage III disease. Gynecol Oncol 60:412-417, 1996
9. Behbakht K, Randall TC, Benjamin I, et al: Clinical characteristics of clear cell carcinoma of the ovary. Gynecol Oncol 70:255-258, 1998
10. Winter WE III, Maxwell GL, Tian C, et al: Prognostic factors for stage III epithelial ovarian cancer: A Gynecologic Oncology Group Study. J Clin Oncol 25:3621-3627, 2007

11. McGuire WP, Hoskins WJ, Brady MF, et al: Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 334:1-6, 1996

12. Piccart MJ, Bertelsen K, James K, et al: Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: Three-year results. J Natl Cancer Inst 92:699-708, 2000

13. Ozols RF, Bundy BN, Greer BE, et al: Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Group study. J Clin Oncol 21:3194-3200, 2003

14. du Bois A, Lück HJ, Meier W, et al: A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 95:1320-1329, 2003

15. Sugiyama T, Fujiwara K. Clear cell carcinoma of the ovary. Am Soc Clin Oncol Ed Book 313-326, 2007

16. Itamochi H, Kigawa J, Sultana H, et al: Sensitivity to anticancer agents and resistance mechanisms in clear cell carcinoma of the ovary. Jpn J Cancer Res 93:723-728, 2002

17. Takano M, Kikuchi Y, Yaegashi N, et al: Clear cell carcinoma of the ovary: A retrospective multicentre experience of 254 patients with complete surgical staging. Br J Cancer 94:1369-1374, 2006

18. Adachi S, Ogasawara T, Yamasaki N, et al: A pilot study of CPT-11 and cisplatin for ovarian clear cell adenocarcinoma. Jpn J Clin Oncol 29:434-437, 1999

19. Takano M, Kikuchi Y, Yaegashi N, et al: Adjuvant chemotherapy with irinotecan hydrochloride and cisplatin for clear cell carcinoma of the ovary. Oncol Rep 16:1301-1306, 2006

20. Takano M, Sugiyama T, Yaegashi N, et al: Progression-free survival and overall survival of patients with clear cell carcinoma of the ovary treated with paclitaxel-carboplatin or irinotecan-cisplatin: Retrospective analysis. Int J Clin Oncol 12: 256-260, 2007

21. Takakura S, Saito M, Ueda K, et al: Irinotecan hydrochloride (CPT-11) and cisplatin as first-line chemotherapy after initial surgery for ovarian clear cell adenocarcinoma. Int Surg 92:202-208, 2007

22. Takakura S, Takano M, Takahashi F, et al: 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. Int J Gynecol Cancer 20:240-247, 2010

23. Pectasides D, Fountzilas G, Aravantinos G, et al: Advanced stage clear-cell epithelial ovarian cancer: The Hellenic Cooperative Oncology Group experience. Gynecol Oncol 102:285-291, 2006

24. Ho CM, Huang YJ, Chen TC, et al: Pure-type clear cell carcinoma of the ovary as a distinct histological type and improved survival in patients treated with paclitaxel-platinum-based chemotherapy in pure-type advanced disease. Gynecol Oncol 94: 197-203, 2004

25. Utsunomiya H, Akahira J, Tanno S, et al: Paclitaxel-platinum combination chemotherapy for advanced or recurrent ovarian clear cell adenocarcinoma: A multicenter trial. Int J Gynecol Cancer 16: 52-56, 2006

26. Omura GA, Brady MF, Homesley HD, et al: Long-term follow-up and prognostic factor analysis in advanced ovarian carcinoma: The Gynecologic Oncology Group experience. J Clin Oncol 9: 1138-1150, 1991

27. Köbel M, Kalloger SE, Santos JL, et al: Tumor type and substage predict survival in stage I and II ovarian carcinoma: Insights and implications. Gynecol Oncol 116:50-56, 2010

28. Jenison EL, Montag AG, Griffiths CT, et al: Clear cell adenocarcinoma of the ovary: A clinical analysis and comparison with serous carcinoma. Gynecol Oncol 32:65-71, 1989

29. Rahman M, Nakayama K, Rahman MT, et al: Clinicopathologic and biological analysis of PIK3CA mutation in ovarian clear cell carcinoma. Hum Pathol 43:2197-2206, 2012

30. Mabuchi S, Kawase C, Altomare DA, et al: mTOR is a promising therapeutic target both in cisplatin-sensitive and cisplatin-resistant clear cell carcinoma of the ovary. Clin Cancer Res 15: 5404-5413, 2009

31. Miyazawa M, Yasuda M, Fujita M, et al: Therapeutic strategy targeting the mTOR-HIF-1alpha-VEGF pathway in ovarian clear cell adenocarcinoma. Pathol Int 59:19-27, 2009

32. Mabuchi S, Kawase C, Altomare DA, et al: Vascular endothelial growth factor is a promising therapeutic target for the treatment of clear cell carcinoma of the ovary. Mol Cancer Ther 9: 2411-2422, 2010

33. Mabuchi S, Altomare DA, Cheung M, et al: RAD001 inhibits human ovarian cancer cell proliferation, enhances cisplatin-induced apoptosis, and prolongs survival in an ovarian cancer model. Clin Cancer Res 13:4261-4270, 2007

34. Kennedy AW, Markman M, Biscotti CV, et al: Survival probability in ovarian clear cell adenocarcinoma. Gynecol Oncol 74:108-114, 1999

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Phase III Trial of Irinotecan Plus Cisplatin Compared With Paclitaxel Plus Carboplatin as First-Line Chemotherapy for Ovarian Clear Cell Carcinoma: JGOG3017/GCIG Trial

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Research Funding: Taiho Pharmaceutical (Inst), Chugai Pharmaceutical (Inst), Shimadzu (Inst), Tsumura (Inst), Sekisui Medical (Inst)

Acknowledgment

We thank the women who participated in the study and their families, the staff of the JGOG3017 Coordinating Center at Kitasato University, JGOG 111 institutions, and the participating GCIGs.

Appendix

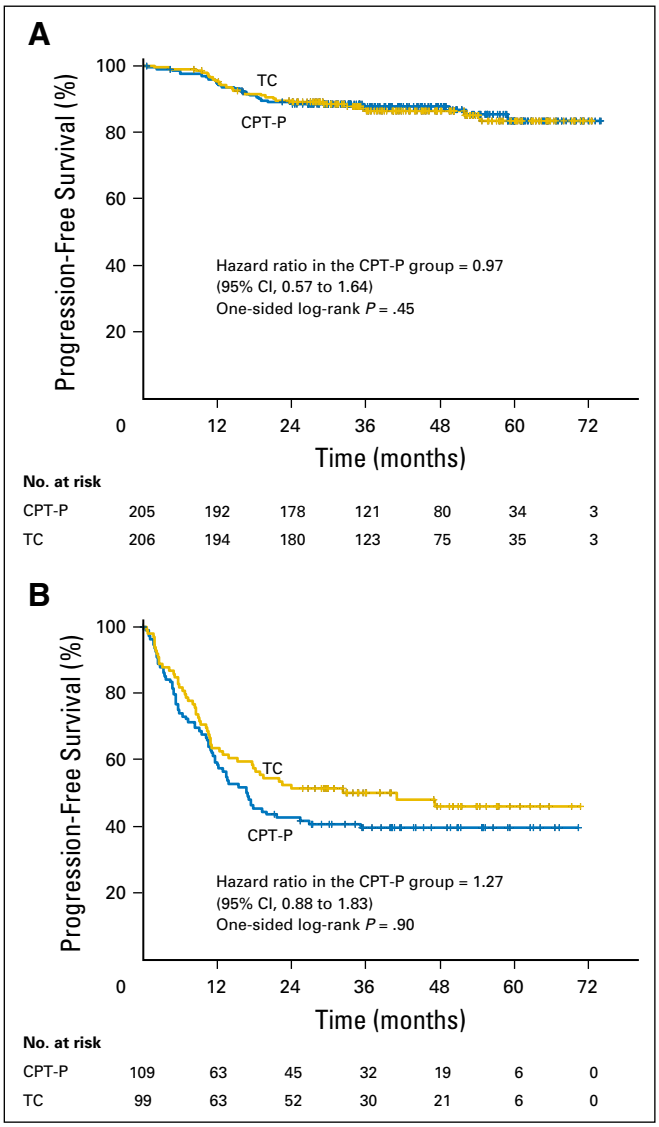

Fig A1. Progression-free survival (PFS) according to stage. PFS in patients with (A) stage I disease and (B) stage II to IV disease. CPT-P, irinotecan plus cisplatin; TC, paclitaxel plus carboplatin.

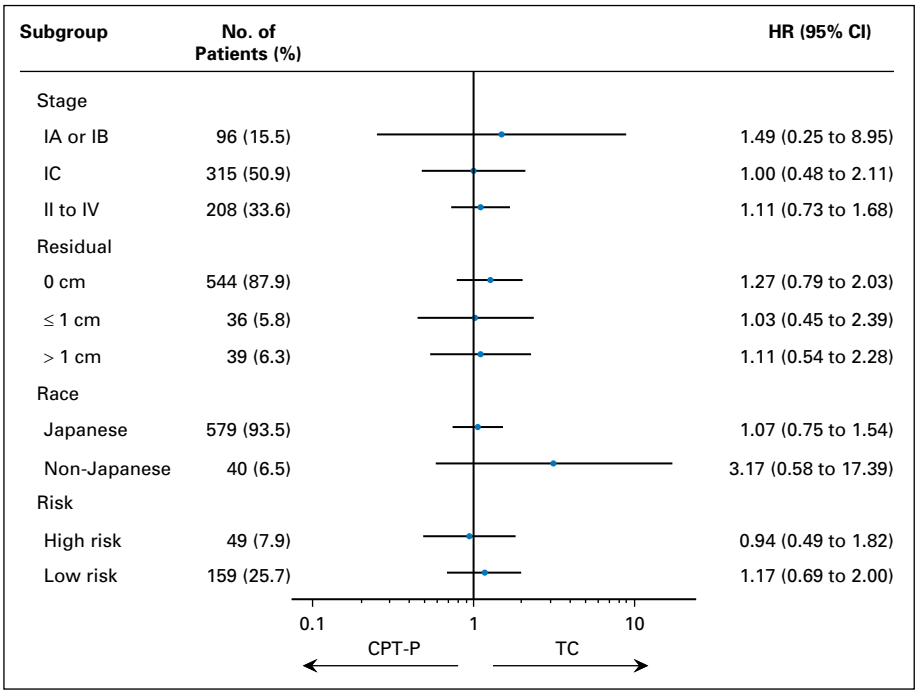

Fig A2. Subgroup analysis of overall survival. CPT-P, irinotecan plus cisplatin; HR, hazard ratio; TC, paclitaxel plus carboplatin.