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ORIGINAL REPORT

Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Cisplatin in Metastatic or Recurrent Cervical Cancer: The Open-Label Randomized Phase III Trial JCOG0505

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See accompanying editorial on page 2125; listen to the podcast by Dr Moore at www.jco.org/podcasts

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ABSTRACT

Purpose

In metastatic or recurrent cervical cancer, cisplatin-based chemotherapy is standard. The JCOG0505 randomized phase III trial evaluated the clinical benefits of carboplatin-based regimen.

Patients and Methods

Eligible patients had metastatic or recurrent cervical cancer and had ≤ one platinum-containing treatment and no prior taxane. Patients were randomly assigned either to conventional paclitaxel plus cisplatin (TP; paclitaxel 135 mg/m^2 over 24 hours on day 1 and cisplatin 50 mg/m^2 on day 2, repeated every 3 weeks) or paclitaxel plus carboplatin (TC; paclitaxel 175 mg/m^2 over 3 hours and carboplatin area under curve 5 mg/mL/min on day 1, repeated every 3 weeks). Primary end point was overall survival (OS). Planned sample size was 250 patients to confirm the noninferiority of TC versus TP with the threshold hazard ratio (HR) of 1.29.

Results

Between February 2006 and November 2009, 253 patients were enrolled. The HR of OS was 0.994 (90% CI, 0.79 to 1.25; noninferiority $P = .032$ by stratified Cox regression). Median OS was 18.3 months with TP versus 17.5 months with TC. Among patients who had not received prior cisplatin, OS was shorter with TC (13.0 *v* 23.2 months; HR, 1.571; 95% CI, 1.06 to 2.32). One treatment-related death occurred with TC. Proportion of nonhospitalization periods was significantly longer with TC ($P < .001$).

Conclusion

TC was noninferior to TP and should be a standard treatment option for metastatic or recurrent cervical cancer. However, cisplatin is still the key drug for patients who have not received platinum agents.

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INTRODUCTION

Most women with metastatic cervical cancer or local recurrence after radiotherapy are candidates for palliative chemotherapy.[1] Historically, cisplatin has been considered the most active agent.[2] Although cisplatin plus paclitaxel has shown no significant overall survival (OS) advantage compared with cisplatin alone, this combination has resulted in a doubling of both response rate (RR) and median progression-free survival (PFS) and had tolerable toxicity.[3,4] Other cisplatin-based combinations have shown no significant benefit over cisplatin plus paclitaxel, which is considered the global standard cytotoxic combination for patients with metastatic or recurrent cervical cancer.[5] However, hydration is required to prevent cisplatin nephrotoxicity,[6] and paclitaxel should be administered over 24 hours to reduce neurotoxicity when combined with cisplatin,[7] necessitating an inpatient hospital stay for each cycle.

Carboplatin has been reported to be a less effective platinum analog than cisplatin for cervical cancer,[7-9] but these agents have not been compared in phase III trials. Carboplatin induces milder nephropathy, less nausea/vomiting, and lower neuropathy than cisplatin.[10] The combination of carboplatin and paclitaxel allows for paclitaxel administration over 3 hours, and carboplatin requires no hydration. In the first multiinstitutional phase II trial of paclitaxel and carboplatin for metastatic or advanced cervical cancer to our knowledge, we found an overall RR of 59% (95% CI, 43 to 75), median PFS of 5.3

months, and median OS of 9.6 months, suggesting that the combination had promising efficacy and feasibility for outpatient treatment.[11]

We report here the results of the first phase III trial to our knowledge to demonstrate survival the noninferiority and clinical benefits of a carboplatin-based regimen compared with cisplatin-based regimen for treatment of metastatic or recurrent cervical cancer.[12]

PATIENTS AND METHODS

Study Design

This multicenter, open-label, randomized phase III trial was designed to evaluate the impact on efficacy, safety, and quality of life (QoL) of carboplatin-based chemotherapy for metastatic or recurrent cervical cancer. The primary end point was OS, defined as the interval between random assignment and death resulting from any cause. Secondary end points included PFS, defined as the interval between random assignment and first documentation of disease progression or death, RR according to RECIST (version 1.0),[13] adverse events, and QoL. In each treatment group, the proportion of nonhospitalization periods compared with planned treatment periods was assessed to evaluate the inconvenience of hospitalization with protocol treatments as an objective measure of QoL.

Patient Population

Eligible patients were between 20 and 75 years of age with histologically confirmed primary stage IVB (including persistent) or first or second recurrent carcinoma of the uterine cervix (squamous cell carcinoma [SCC], adenocarcinoma, or adenosquamous carcinoma) not amenable to curative surgery or radiotherapy (definition provided in Appendix, online only). Other inclusion criteria were as follows: ≤ one prior platinum-based chemotherapy, including concurrent chemoradiotherapy; no prior chemotherapy with taxanes; Eastern Cooperative Oncology Group performance status[14] ≤ 2; and adequate liver, renal, and bone marrow function. Exclusion criteria were: neurologic disturbance with functional disorder, hypersensitivity to alcohol, symptomatic CNS metastasis, or active clinically significant cardiovascular disease.

All patients provided written informed consent before enrollment. The trial was conducted in accordance with the Declaration of Helsinki. The trial protocol was approved by the Japan Clinical Oncology Group (JCOG) Protocol Review Committee and the institutional review board of each participating institution before patient enrollment.

Treatment

Patients were randomly assigned to receive either paclitaxel plus cisplatin (TP) or paclitaxel plus carboplatin (TC) within 1 week after enrollment. The JCOG Data Center performed random assignment at a ratio of 1:1 using the minimization method to balance institution, performance status (0 to 1 *v* 2), tumor histology (SCC *v* non-SCC), and presence of tumors outside the prior irradiation field (yes *v* no). The TP regimen consisted of paclitaxel 135 mg/m^2 over 24 hours intravenously (IV) on day 1, followed by cisplatin 50 mg/m^2 IV on day 2. This regimen has been used in prior Gynecologic Oncology Group (GOG) trials.[3,4] The TC regimen consisted of paclitaxel 175 mg/m^2 over 3 hours IV on day 1, immediately followed by a 1-hour IV infusion of carboplatin at area under the curve of 5 mg/mL per minute on the same day. The carboplatin dose in milligrams was calculated with the Calvert formula,[15] using creatinine clearance instead of glomerular filtration rate. Creatinine clearance was estimated using the Cockcroft-Gault formula.[16] Irrespective of calculated doses, the maximum absolute dose was limited to 1,000 mg in consideration of patients with low muscle mass resulting from debilitation or old age. The TC regimen mirrored that in our preceding phase II trial[11] and

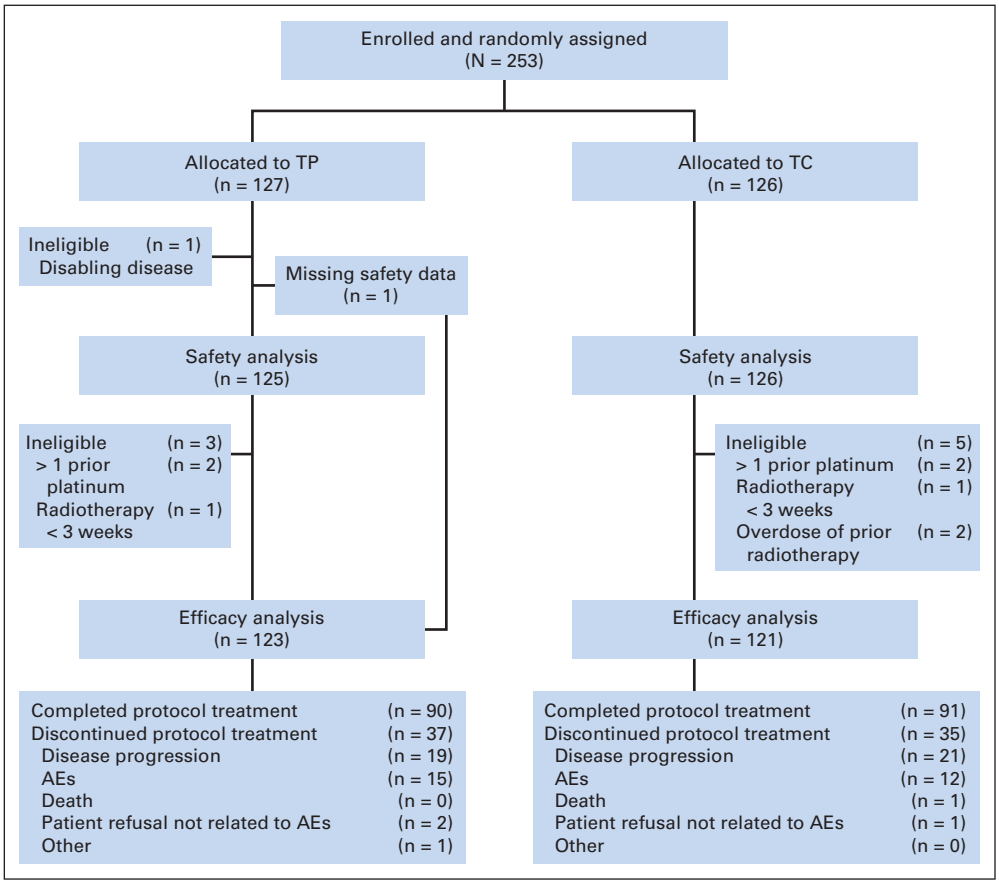

Fig 1. Patient disposition. AE, adverse event; TC, paclitaxel plus carboplatin; TP, paclitaxel plus cisplatin.

could be administered on an outpatient basis when deemed appropriate. Both regimens were repeated every 3 weeks until disease progression or unacceptable toxicity or for a maximum of six cycles so that the QoL of incurable patients would not be adversely affected by cumulative toxicity. Patients were observed monthly after protocol treatment until death.

Protocol-specified treatment modifications were permitted in the event of predefined toxic events. Treatment could be delayed for a maximum of 3 weeks. Doses of all agents were reduced by 20% to 25% in the event of thrombocytopenia grade ≥ 3, grade 3 febrile neutropenia, or grade 3 vomiting. In patients with serum creatinine elevation or grade 2 to 3 ototoxicity, cisplatin dose was reduced by 20%. In cases of grade 2 neurotoxicity, both treatments were delayed until recovery to grade ≤ 1, and paclitaxel dose was reduced by approximately 20% to 25%. The data and safety monitoring committee monitored study progress and safety data on a regular basis.

Study Assessments

Radiographic disease measurements were required at baseline and at least after every three cycles, using the same assessment technique (preferably computed tomography). Tumor response was evaluated according to RECIST (version 1.0).[13] Before each treatment cycle and within 30 days after completing treatment, safety assessments were performed according to the Common Terminology Criteria for Adverse Events (version 3.0). For each patient, the proportion of nonhospitalization periods was calculated as the nonhospitalization days during the six treatment cycles divided by the planned treatment days (21 × 6 days).

Statistical Design and Analysis

Initially, with an accrual time of 2.5 years and minimum follow-up period of 1 year, the required number of OS events was 209 and the planned sample size was 250 according to the Schoenfeld and Richter method[17] to confirm the noninferiority of TC compared with TP, with a one-sided α level of 0.05 and power of at least 70%, with noninferiority margin of 1.29, corresponding to 2 months in OS, assuming a median OS in the TP group of 9 months based on outcome in the GOG 169 trial (SCC only).

OS and PFS were estimated using the Kaplan-Meier method.[18] The primary analysis of OS was conducted using a stratified Cox regression model. We had planned to use performance status (0 to 1 *v* 2), tumor histology (SCC *v* non-SCC), and presence of tumors outside the prior irradiation field (yes *v* no) as stratification factors, considering the number of participants and events per stratum for performance status and tumor histology. However, we changed the plan to use presence of tumors outside the prior irradiation field (yes *v* no)[19,20] as the only stratification factor; it was described in the statistical analysis plan, which was finalized in advance to carry out confirmatory analysis. Noninferiority of OS would be confirmed if the upper limit of the 90% CI for the HR were < 1.29. A Cox proportional hazards model was used to estimate HRs.[21]

Efficacy analysis was conducted for all eligible patients, and safety analysis was conducted for all treated patients. A one-sided *P* value of .05 was considered to indicate statistical significance, and 95% CIs were used unless otherwise stated. The proportion of grade 3 or 4 adverse events was compared between treatment groups using Fisher's exact test. The proportion of nonhospitalization periods relative to planned treatment periods was calculated for each patient, and the distributions of an individual patient's proportion for each treatment group were compared using the Wilcoxon rank sum test. Subgroup analyses were performed to assess the heterogeneity of treatment effects. All subgroups were prespecified and shown in a forest plot.[22] The planned interim analysis was conducted when half of the planned sample size was reached. Multiplicity for the primary end point was adjusted using the O'Brien-Fleming–type alpha spending function.[23] If it was evident that the primary objective of the trial had been attained, the study would be closed, and the results would be presented and published immediately.

RESULTS

Patient Population

Between February 2006 and November 2009, a total of 253 patients were enrolled. Randomly assigned patients included 127 patients in the TP group and 126 patients in the TC group. Patient disposition is shown in Figure 1. Baseline characteristics were well balanced between the two treatment groups and are summarized in Table 1.

Efficacy

The data cutoff date for final analysis was November 21, 2011. Median duration of follow-up was 17.6 months for all 244 eligible patients, and 204 events for OS were observed.

The study met its primary objective, demonstrating a significant noninferiority in OS of TC compared with TP (hazard ratio [HR], 0.994; multiplicity-adjusted 90% CI, 0.789 to 1.253 [< 1.29]; one-sided $P = .032$; Fig 2A). Median OS was 18.3 months (95% CI, 16.1 to 22.9 months) in the TP group and 17.5 months (95% CI, 14.2 to 20.3 months) in the TC group. In a post hoc attempt to identify factors associated with better OS, we analyzed treatment effects in subgroups. Among those patients who had not received prior cisplatin-based chemotherapy (including carboplatin or nedaplatin for one to two patients in each group), median OS was shorter in the TC group (13.0 months; 95% CI, 10.0 to 20.4 months) than in the TP group (23.2 months; 95% CI, 17.4 to 27.4 months; HR, 1.571; 95% CI, 1.062 to

Table 1. Baseline Patient Characteristics

Characteristic	TP (n = 127) No.	TP (n = 127) %	TC (n = 126) No.	TC (n = 126) %
Age, years				
Median	53		53	
Range	29-74		22-72	
ECOG performance status*				
0	98	77	96	76
1	27	21	27	21
2	2	1.6	3	2.4
Histologic type*				
Squamous cell carcinoma	106	83	105	83
Adenosquamous cell carcinoma	3	2.4	4	3.2
Adenocarcinoma	18	14	17	13
Disease status				
IVB or persistent	27	21	24	19
First recurrence	82	65	85	67
Second recurrence	18	14	17	13
Prior irradiation	100	79	108	86
Tumors outside prior irradiated field*				
Yes	81	64	76	60
No	46	36	50	40
Prior platinum chemotherapy				
Yes	61	48	72	57
Cisplatin	54	43	60	48
Carboplatin	0	0	2	2
Other	7	6	10	8
No	66	52	54	43
Platinum-free interval, months†				
< 6	20	16	13	10
≥ 6 and < 12	20	16	24	19
≥ 12	21	17	35	28
None	66	52	54	43

Abbreviations: ECOG, Eastern Cooperative Oncology Group; TC, paclitaxel plus carboplatin; TP, paclitaxel plus cisplatin.
*Stratification factor.
†From last platinum to subsequent disease progression.

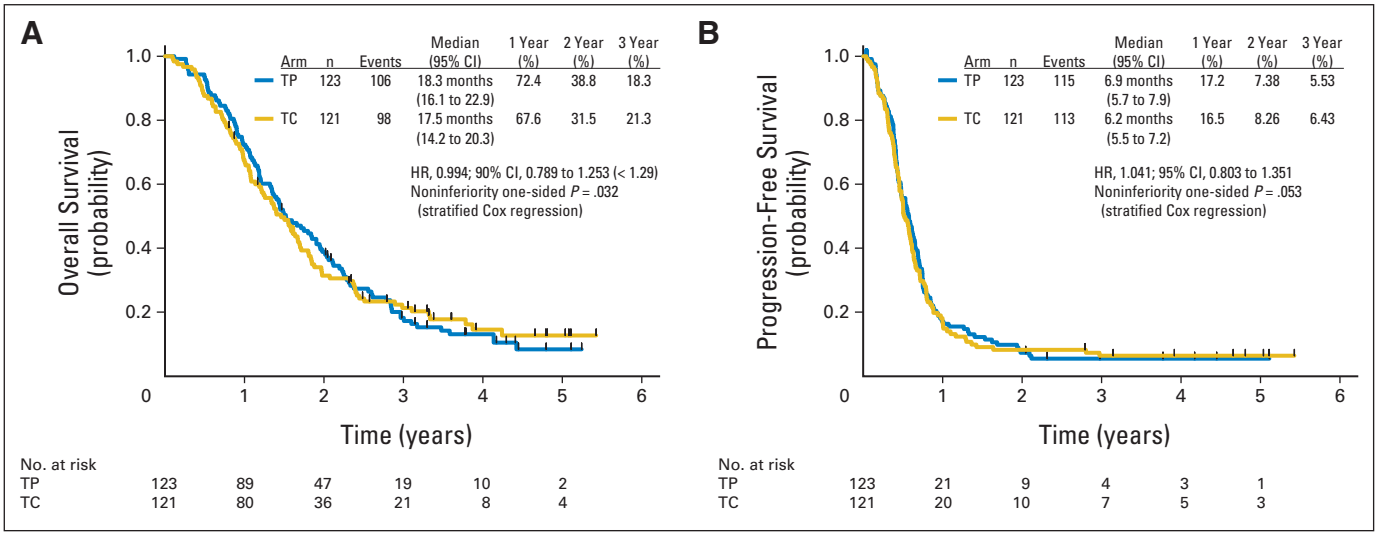

Fig 2. (A) Overall and (B) progression-free survival. HR, hazard ratio; TC, paclitaxel plus carboplatin; TP, paclitaxel plus cisplatin.

2.324). There was no remarkable interaction among the other subgroups (Fig 3).

Analysis of PFS was based on 228 events among the 244 eligible patients. Median PFS was 6.9 months (95% CI, 5.7 to 7.9 months) in the TP group and 6.2 months (95% CI, 5.5 to 7.2 months) in the TC group (HR, 1.041; 95% CI, 0.803 to 1.351; Fig 2B).

Among the efficacy population, 102 of 123 patients in the TP group and 99 of 121 patients in the TC group had measurable lesions and were evaluated according to RECIST. Complete response rate was 3.9% in the TP group and 7.1% in the TC group. The RR, defined as the percentage of patients who had a complete or partial response, was 58.8% (95% CI, 48.6 to 68.5%) in the TP group and 62.6% (95% CI, 52.3 to 72.2%) in the TC group (Fisher's exact test $P = .665$).

Treatment Exposure

Median number of treatment cycles in all treated patients was six (range, one to six cycles) in both treatment groups. The proportion of patients who completed the entire treatment protocol was 70.9% in the TP group and 72.2% in the TC group. Median relative dose-intensities of paclitaxel and cisplatin in the TP group were 97.8% and 98.4%, respectively; those of paclitaxel and carboplatin in the TC group were 99.8% and 99.9%, respectively.

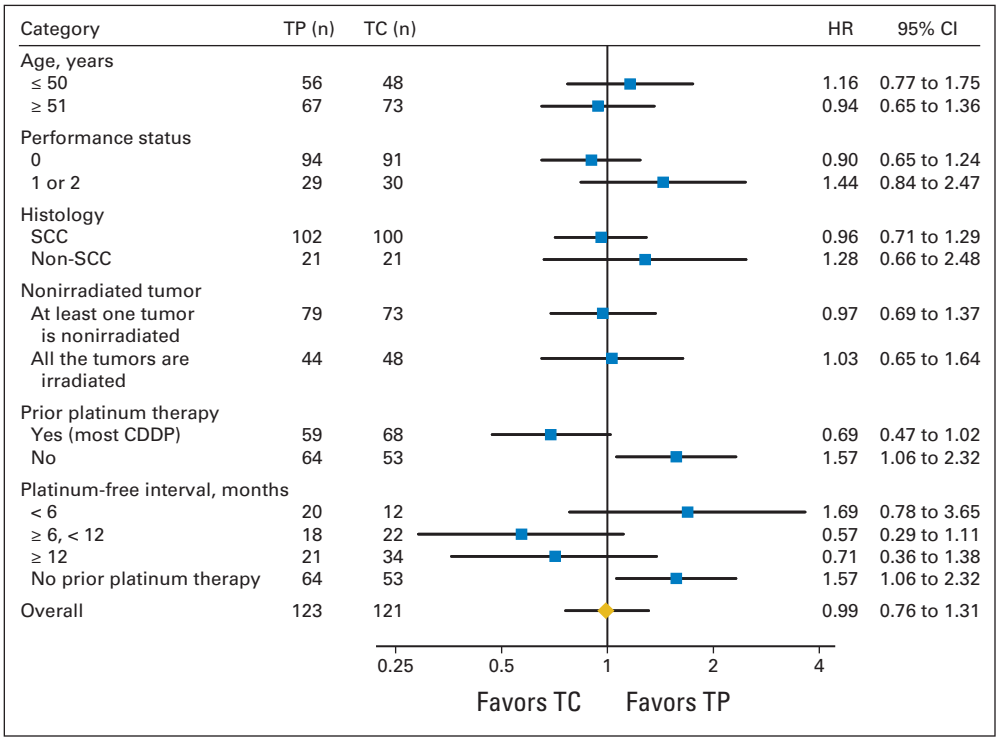

Fig 3. Subgroup analysis of overall survival. Horizontal lines represent hazard ratio (HRs; with 95% CIs) from final analysis. CDDP, cisplatin; SCC, squamous cell carcinoma; TC, paclitaxel plus carboplatin; TP, paclitaxel plus cisplatin.

Table 2. Summary of Grade ≥ 3 (and selected grade ≥ 2) AEs of Special Interest*

AE	TP (n = 125)		TC (n = 126)	
	No.	%	No.	%
Neutropenia†				
Grade 3 to 4	106	85.5	96	76.2
Grade 4	93	75.0	57	45.2
Febrile neutropenia	20	16.0	9	7.1
Anemia	39	31.2	56	44.4
Thrombocytopenia	4	3.2	31	24.6
Creatinine				
Grade 2	9	7.2	6	4.8
Grade 3 to 4	3	2.4	0	0
Infection	6	4.8	6	4.8
Nausea/vomiting	8	6.4	4	3.2
Fatigue	5	4.0	10	7.9
Sensory neuropathy	0	0	6	4.8

Abbreviations: AE, adverse event; TC, paclitaxel plus carboplatin; TP, paclitaxel plus cisplatin.
*Most of the events listed are those that occurred in > approximately 5% of patients in either group.
†Because of missing data in TP group, n = 124.

Safety

Only one patient died as a result of interstitial pneumonitis related to protocol treatment in the TC group. One patient in the TC group died before completion of the treatment cycle, but the data and safety monitoring committee judged death unlikely to have been related to treatment. The proportions of patients who terminated treatment because of intolerable adverse events were similar: 9.5% in the TC group and 11.8% in the TP group. No patient in either group experienced grade 4 hypersensitivity reactions resulting from paclitaxel. Treatment-related grade 3 or 4 adverse events occurring in more than approximately 5% of patients in either treatment group are summarized in Table 2. Incidences of grade 4 neutropenia (75.0% *v* 45.2%; $P < .001$), grade 3 to 4 febrile neutropenia (16.0% *v* 7.1%; $P = .031$), creatinine elevation (2.4% *v* 0.0%; $P = .122$), and nausea/vomiting (6.4% *v* 3.2%; $P = .254$) tended to be higher in the TP group, whereas incidences of thrombocytopenia and sensory neuropathy tended to be higher in the TC group. Blood transfusions were administered to 18.3% of patients who received TC and 8.7% of patients who received TP; platelet transfusions were administered to 6.3% of patients who received TC and only 0.8% of patients who received TP. The mean proportion of nonhospitalization periods relative to planned treatment periods, which was used as an objective measure of QoL in this study, was significantly greater in the TC group (61.9% *v* 46.4%; $P < .001$).

DISCUSSION

The JCOG0505 trial met its primary objective, demonstrating statistically significant noninferiority in terms of OS (HR, 0.994; multiplicity-adjusted 90% CI, 0.789 to 1.253 [< 1.29]) of TC compared with standard TP therapy for incurable metastatic or recurrent cervical cancer. The clinical benefits of carboplatin-based chemotherapy for cervical cancer affect current evidence-based clinical practice for the disease.

The patient selection criteria in our study included non-SCC histology and ≤ one prior platinum-based chemotherapy, including concurrent chemoradiotherapy, because the proportion of those patients has grown steadily in recent years. Neither tumor histology nor presence of tumors outside the prior irradiation field had prognostic significance with respect to OS, which is different from the findings of other studies.[19,20] In contrast, we found a large treatment effect with TP therapy in patients who had not received prior platinum treatment (usually cisplatin-based chemoradiotherapy), and TC was more effective than TP for patients with a history of platinum administration. Therefore, TP remains the standard regimen for patients without prior cisplatin-based therapy, such as those with primary stage IVB cervical cancer with adequate renal function. Two recent phase III trials found that prior concurrent chemoradiotherapy was associated with decreased efficacy of single-agent treatment with cisplatin.[4,24] One explanation for these subsequent treatment effects is cisplatin resistance, which is biologically probable.[25,26] One recent phase III trial found no superiority of a nonplatinum combination.[27] Therefore, other platinums with no cross resistance with cisplatin are required for recurrent cervical cancer, and carboplatin may be one such agent. This finding should be evaluated in additional investigations.

Carboplatin monotherapy was shown to have lower efficacy (RR, 15% to 28.2%; response duration, 2.0 to 6.75 months) than cisplatin monotherapy,[7-9] but these agents have not been compared in phase III trials. Conversely, TC is considered an effective regimen based on retrospective studies and our phase II trial.[11,28,29] In the present trial and those recent studies, the dose of carboplatin (area under curve 5 every 3 weeks), which should be calculated from renal function,[15] may have resulted in more platinum exposure than in previous trials (340 to 400 mg/m^2 every 4 weeks).[7-9] It is unlikely that a paclitaxel dose of 175 mg/m^2 administered over 3 hours IV (TC regimen) is superior to 135 mg/m^2 over 24 hours IV (TP regimen) based on the results of a randomized controlled trial.[6] Using the same trial design as JCOG0505, GOG 158 also demonstrated that TC was not inferior to TP for advanced ovarian cancer.[30] Therefore, we suggest that carboplatin at a dose based on renal function has efficacy similar to that of cisplatin for metastatic or recurrent cervical cancer. This has implications not only for incurable patients but also for primary patient cases involving decreased renal function because of hydronephrosis.

Median OS after TP therapy in our current trial (18.3 months) compares favorably with those reported in other phase III trials (9.7 to 14.3 months) with the same therapy,[3,4,27] whereas median PFS of 6.9 months in our trial was similar to those in others (4.8 to 5.9 months).[3,4,27] Therefore, we speculate that the greater use of postprogression treatment might have prolonged OS in our current trial compared with our previous phase II trial, based simply on similar results observed in clinical trials of other cancer types conducted in Japan and even in the GOG studies, despite an increasing penetration rate of concurrent chemoradiotherapy. Moreover, bevacizumab combined with TC or TP could improve prognosis according to the most recent phase III trial in this setting (GOG 240).[27]

The toxicities reported in our study were not unexpected, given those in previous trials.[3,5,6,11] TC was associated with a higher incidence of sensory neuropathy, but there were no irreversible treatment-related adverse events. Approximately 70% of patients in both groups completed the planned therapy, doses were well

tolerated, and good compliance was demonstrated for both protocol treatments.

Incidences of febrile neutropenia and nausea/vomiting tended to be higher in the TP group. In addition, it was expected that patient discomfort would not be evaluated in a patient-reported manner of QoL scoring between the two treatment groups. The TC regimen has the advantages of not requiring patient hydration and permitting paclitaxel administration in an outpatient setting. Examination of hospitalization time for each treatment protocol, which represented an objective measure of QoL, revealed that patients treated with TC spent less time in the hospital. The shorter duration of treatment time might increase cost effectiveness. The proportion of nonhospitalization periods relative to planned treatment periods could have been even larger than the reported 61.9% in the TC group, because physicians were free to decide on the necessity of hospitalization for TC therapy according to the Japanese medical insurance system.

In our trial, the noninferiority margin of 1.29 was determined based on a tradeoff between efficacy and patients' burden in terms of toxicity and duration of hospitalizations—a tradeoff was realized with TC—and corresponds to negate the 2-month reduction in median OS for TC in comparison with OS for TP, which was expected to be 9 months. As a result, given that patients can be treated with less toxic and less inconvenient methods using TC, the rationale of setting the margin at 1.29 is considered to have been adequate. In summary, to our knowledge, JCOG0505 is the first trial demonstrating significant noninferiority of carboplatin-based chemotherapy in terms of OS and clinical benefits for cervical cancer. Therefore, TC should be a standard treatment option for metastatic or recurrent cervical cancer. However, cisplatin is still the key drug for patients who have not received prior cisplatin-based treatment, such as those with primary stage IVB cervical cancer.

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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Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Friedlander M, Grogan M: Guidelines for the treatment of recurrent and metastatic cervical cancer. Oncologist 7:342-347, 2002
2. Thigpen JT, Vance R, Puneky L, et al: Chemotherapy as a palliative treatment in carcinoma of the uterine cervix. Semin Oncol 22:16-24, 1995 (suppl 3)
3. Moore DH, Blessing JA, McQuellon RP, et al: Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study. J Clin Oncol 22:3113-3119, 2004
4. Monk BJ, Sill MW, McMeekin DS, et al: Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: A Gynecologic Oncology Group study. J Clin Oncol 27:4649-4655, 2009
5. Calvert AH, Harland SJ, Newell DR, et al: Early clinical studies with cis-diammine-1, 1-cyclobutane dicarboxylate platinum II. Cancer Chemother Pharmacol 9:140-147, 1982
6. Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, et al: European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: High-dose versus low-dose and long versus short infusion. J Clin Oncol 12:2654-2666, 1994
7. Arseneau J, Blessing JA, Stehman FB, et al: A phase II study of carboplatin in advanced squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study. Invest New Drugs 4:187-191, 1986
8. Weiss GR, Green S, Hannigan EV, et al: A phase II trial of carboplatin for recurrent or metastatic squamous carcinoma of the uterine cervix: A Southwest Oncology Group study. Gynecol Oncol 39:332-336, 1990
9. McGuire WP 3rd, Arseneau J, Blessing JA, et al: A randomized comparative trial of carboplatin and iproplatin in advanced squamous carcinoma of the uterine cervix: A Gynecologic Oncology Group study. J Clin Oncol 7:1462-1468, 1989
10. Anderson H, Wagstaff J, Crowther D, et al: Comparative toxicity of cisplatin, carboplatin (CBDCA) and iproplatin (CHIP) in combination with cyclophosphamide in patients with advanced epithelial ovarian cancer. Eur J Cancer Clin Oncol 24:1471-1479, 1988
11. Kitagawa R, Katsumata N, Ando M, et al: A multi-institutional phase II trial of paclitaxel and carboplatin in the treatment of advanced or recurrent cervical cancer. Gynecol Oncol 125:307-311, 2012
12. Saito I, Kitagawa R, Fukuda H, et al: A phase III trial of paclitaxel plus carboplatin versus paclitaxel plus cisplatin in stage IVB, persistent or recurrent cervical cancer: Gynecologic Cancer Study Group/Japan Clinical Oncology Group study (JCOG0505). Jpn J Clin Oncol 40:90-93, 2010
13. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. European Organisation for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-216, 2000
14. Oken MM, Creech RH, Tormey DC, et al: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982
15. Calvert AH, Newell DR, Gumbrell LA, et al: Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748-1756, 1989
16. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. Nephron 16:31-41, 1976
17. Schoenfeld DA, Richter JR: Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. Biometrics 38:163-170, 1982
18. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958
19. Brader KR, Morris M, Levenback C, et al: Chemotherapy for cervical carcinoma: Factors determining response and implications for clinical trial design. J Clin Oncol 16:1879-1884, 1998
20. Potter ME, Hatch KD, Potter MY, et al: Factors affecting the response of recurrent squamous cell carcinoma of the cervix to cisplatin. Cancer 63:1283-1286, 1989
21. Royston P, Parmar MK: Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modeling and estimation of treatment effects. Stat Med 21:2175-2197, 2002
22. Early Breast Cancer Trialists' Collaborative Group: Introduction and Methods in Treatment of Early Breast Cancer: Worldwide Evidence 1985-1990 (volume 1). Oxford, United Kingdom, Oxford University Press, 1990
23. Lan KKG, DeMets DL: Discrete sequential boundaries for clinical trials. Biometrika 70:659-663, 1983
24. Long HJ 3rd, Bundy BN, Grendys EC Jr, et al: Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: A Gynecologic Oncology Group study. J Clin Oncol 23:4626-4633, 2005
25. Kuo DY, Blank SV, Christos PJ, et al: Paclitaxel plus oxaliplatin for recurrent or metastatic cervical cancer: A New York Cancer Consortium study. Gynecol Oncol 116:442-446, 2010
26. Rabik CA, Dolan ME: Molecular mechanisms of resistance and toxicity associated with platinating agents. Cancer Treat Rev 33:9-23, 2007

27. Tewari KS, Sill MW, Long HJ 3rd, et al: Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med 370:734-743, 2014

28. Tinker AV, Bhagat K, Swenerton KD, et al: Carboplatin and paclitaxel for advanced and recurrent cervical carcinoma: The British Columbia Cancer Agency experience. Gynecol Oncol 98:54-58, 2005

29. Pectasides D, Fountzilas G, Papaxoinis G, et al: Carboplatin and paclitaxel in metastatic or recurrent cervical cancer. Int J Gynecol Cancer 19:777-781, 2009

30. 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

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Appendix

Definition of Cervical Cancer Not Amenable to Curative Surgery or Radiotherapy

If at least one of the following conditions are present, surgical resection cannot be safely performed:

- There is at least one metastatic lesion outside the pelvic cavity, excluding the para-aortic lymph node (LN) and/or inguinal LN.
- There is no metastatic lesion outside the pelvic cavity, excluding the para-aortic LN and/or inguinal LN, and some of the lesions have been irradiated.
- All lesions are localized inside the pelvic cavity, and some of them have been irradiated.

Definition of Progression

For patients with a measurable lesion at the time of registration, progression is determined by the presence of any of the following conditions according to (RECIST):

- At least a 20% increase in the sum of the longest diameters (LDs) of the target lesions, with the smallest recorded LD taken as baseline, since treatment started (including relapse).
- The appearance of $\geq$ one new lesion.
- Death resulting rrom disease without prior objective documentation of progression.
- Unequivocal progression of existing nontarget lesions (including relapse).

Of note, when the sum of the LDs is $\leq$ 20 mm before and after evaluation, the definition of progression as described is not adopted.

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