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Original Article

Prospective cohort study to evaluate the efficacy of taxane plus platinum and CPT-11plus platinum regimes and to identify prognostic risk factors in cervical cancer patients

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Abstract: Objective: This study was designed to evaluate the response, toxicity and survival of taxanes plus platinum (TP) and CPT-11plus platinum (CP) as neoadjuvant chemotherapies with previously untreated cervical cancer, and to identify prognostic risk factors in these patients. Methods: A cohort study was performed to evaluate the result of TP and CP regimes in the treatment of cervical cancer patients. Results: The study included 567 patients with locally advanced cervical cancer (LACC) staged as FIGO IB-IIB in our clinical departments. Clinical response was found in 76.1% and 78% of patients in the TP and CP arms, respectively, and no treatment-related deaths were reported. During the follow-up period, disease-free survival (DFS) and overall survival (OS) for the TP and CP arms were not different (P = 0.384 for DFS, P = 0.800 for OS). The CP regime showed higher survival rate for endophytic growth style (P = 0.013 for DFS, P = 0.027 for OS). The CP regime also showed higher DFS and OS for G2 tumor (P = 0.027 for DFS, P = 0.032 for OS). In multivariate cox's proportional hazards regression model, the average death rates were much greater in the non-responder group (HR, 2.68), in the older (> 44 years) group (HR, 2.51), and in the FIGO stage II b patients (HR, 2.84). Conclusions: The CP regime showed higher survival rate for endophytic growth style or G2 tumor. Clinical response, age and FIGO stage were independent prognostic risk factors in this study for both DFS and OS.

Keywords: Cervical cancer, neoadjuvant chemotherapy, platinum, taxane, irinotecan

Introduction

Cervical cancer is the third-most commonly diagnosed cancer and the fourth leading cause of cancer deaths in females worldwide, accounting for 9% (529,800) of total new cancer cases and 8% (275,100) of total cancer deaths among females in 2008 [1]. More than 85% of these cases and deaths occurred in developing countries, and approximately 15% of all cervical cancers occurred in women under the age of 40. Traditional treatment for cervical cancer consists of radical surgery or radiotherapy without sparing fertility, which leads to psychosexual dysfunction and decreased quality of life.

Neoadjuvant chemotherapy (NACT) has emerged as a promising step forward in the management of locally advanced cervical cancer (LACC). Many trials showed a significant increase in survival after subjection to NACT com-

pared with those treated with primary radiotherapy or surgery. Compared with irradiation, this treatment benefited patients by reducing toxic reactions and improving the quality of life of the patients [2]. When administered before surgery, chemotherapy may shrink tumors, eradicate metastases, facilitate surgery and increase the surgery rate with an improved prognosis [3]. Furthermore, NACT allows clinical and pathologic assessment of a tumor response to a particular chemotherapeutic regimen and, hence, provides an opportunity to optimize therapy. This tempting result of NACT may open a completely new era for LACC treatment.

Since the 1990s, new toxic drugs have been investigated as new therapeutic approaches in cervical cancer research. Platinum was considered the single-most active cytotoxicagentand has been used in an effective neoadjuvant setting in cervical cancer. Platinum-based combination therapies were also used to increase the response rate and long-term survival benefit.

Irinotecan, which is a camptothecin analog, exerts antitumoral activity through its active metabolite SN-38 by inhibiting the intranuclear enzyme topoisomerase 1 and subsequently blocking DNA replication. The compound was initially introduced for LACC treatment and then incorporated with a number of combination chemotherapeutic regimens, included platinum, which presented many promising results and much proof [4, 5]. The CP regime has long been used as a treatment method for LACC [6-8].

Taxanes have anti-neoplastic action through the unique cytotoxic mechanism of poisoning the mitotic spindle by forming tubulin polymers and stabilizing the resulting complex. The antitumor activity of taxanes has been demonstrated in a variety of malignancies, including leukemias, carcinosarcoma and lung tumor. Although dose-limiting toxicity such as myelosuppression exists, taxanes are usually safe. The results of published trials in patients with cervical cancer have also suggested that paclitaxel is a relatively active and well-tolerated drug [9]. The combination of taxane and platinum (TP regime) has made a significant contribution to the treatment of cervical cancer in adjuvant and metastatic settings [10-12].

Therapeutic development makes the identification of new agent combinations with superior clinical effects a principal goal of chemotherapy investigation because the anticancer activity and side effects must be weighted carefully. To facilitate clinician swith the most suitable chemotherapy drug in the treatment of LACC, we designed this study to evaluate the antitumor activity and tolerance of the combination of CPT-11plus platinum (CP) and that of taxanes plus platinum (TP).

Methods

Eligibility

This was a prospective cohort study, and the registration number at Clinical trials.gov was NCT01628757. Eligible patients were diagnosed with cervical cancer by pathological experts according to cervical biopsy and staged as IB to IIB by clinicians according to the International Federation of Gynecology and Obstetrics (FIGO). The exclusion criteria included preexisting sensory or motor neuropathy greater than WHO grade 1, a history of myocardial infarction and cardiac insufficiency > grade 3 (New York Heart Association scale). Patients previously treated for cervical cancer (i.e., surgery, chemotherapy or radiotherapy) and a past or current history of other neoplasm were excluded. Patients with active infectious disease or other medically complicating condition were excluded. Women who were pregnant or lactating were also excluded from this study.

The clinical investigation followed the Declaration of Helsinki and was approved by the ethics committee at each participating center, and all eligible patients gave written informed consent before entering this study. The primary aim of this study was to compare the overall survival (OS) between the two regimes. The secondary aim of this study was to compare the response rate and disease-free survival (DFS).

Treatment and dose modifications

The patients were required to have an absolute neutrophil count of more than 1.5×10^9/L, a white count of more than 3.0×10^9/L and a platelet count of more than 100×10^9/L at the beginning of treatment; otherwise, treatment was delayed until the required blood cells had been restored. At the time of re-treatment, drug

Table 1. Clinical characteristics

Characteristic	TP (n = 392)		CP (n = 175)		P*
	No.	%	No.	%	
Age (25th-75th percentiles) (year)					
Median	44		44		
Range	38-49		38-49		
Tumor size (25th-75th percentiles) (cm)					
Median	4		4		
Range	3-5		3-5		
Growth style					
Exophytic	289	74.5	137	79.2	0.228
Endophytic	99	25.5	36	20.8	
Tumor grade					0.628
G1	28	7.1	10	5.7	
G2	169	43.1	76	43.4	
G3	113	28.8	58	33.1	
unknown	82	20.9	31	17.7	
FIGO stage					0.093
Ib	104	26.5	57	32.6	
IIa	79	20.2	42	24.0	
IIb	209	53.3	76	43.4	
Cell type					0.704
Squamous	342	87.2	157	89.7	
Non-squamous	47	12.0	17	9.7	
Unkown	3	0.8	1	0.6	
Menopausal status					0.107
Postmenopausal	96	24.5	37	21.1	
Premenopausal	288	73.5	129	73.7	
Unknown	8	2.0	9	5.1	

Clinical characteristics for both arms. And the comparation showed no statistically significant difference. Abbreviations: TP, Taxanesplus platinum; CP, CPT-11plus platinum; FIGO, International Federation of Gynecology and Obstetrics. *P < 0.05 indicates statistical significance.

Table 2. Clinical response to neoadjuvant TP or CP chemotherapy

Response	TP arm (n = 354)		CP arm (n = 162)		P
	No.	%	No.	%	
CR	47	13.5	20	12.6	0.228
PR	218	62.6	104	65.4	
SD	77	22.1	28	17.6	
PD	6	1.7	7	4.4	
Undetermined	6		3		

No statistically significant difference for clinical response was found between neoadjuvant TP or CP chemotherapy. Abbreviations: TP, taxanesplus platinum; CP, CPT-11plus platinum; CR, clinical rsponse; PR, partial response; SD, stable disease; PD, progressive disease.

doses were adjusted according to nadir blood cell counts and rena land hepatic toxicity. The platinum dose was suspended for the present cycle if grade 3 to 4 renal or hepatic toxicity arose on the scheduled day of re-treatment and was not given until it returned to the required level. Platinum and irinotecan doses were reduced by 20% for grade 3 to grade 4 interval hematologic toxicity, and dose reductions were not allowed for mild (Grade 1 or 2) interval hematologic toxicity. Toxicity and adverse effects were monitored by documenting any serious adverse events while in the study (day beginning from random assignment until day 28 after final surgery). Granulocyte colony-stimulating factor (G-CSF) was not used unless Grade 3 or 4 hematologic toxicity occurred. The tumor status was verified clinically, and an EKG was performed when each treatment began. Ultrasound of the tumor and pelvic condition was scheduled after each cycle to control for progressive disease in all patients. If the tumors were considered operable, radical surgery was performed within 4 weeks after completion of the last scheduled chemotherapy cycle. Otherwise, the patients underwent concurrent chemoradiotherapy.

Evaluation of the short-term response

Colombo et al demonstrated that achievement of an OPT was a surrogate end point of survival [13]. A pathological complete response (pCR) was defined as the absence of a tumor with no involved lymph node in the final surgical sample. An OPT was defined as pCR or a micro invasive residual lesion less than 3 mm that included in situ carcinoma (PR1). A suboptimal response consisted of persistent residual disease with more than 3 mm stromal invasion of the surgical specimen (PR2) [13-15]. Pathologists were blinded to the patient treat-

Table 3. Pathological result after neoadjuvant TP or CP chemotherapy

Pathological result	TP (n = 320)		CP (n = 150)		P*
	Positive No.	%	Positive No.	%	
Lymph node metastasis	64	20.1	26	17.4	0.494
Parametrial infiltration	7	2.2	5	3.3	0.090
Vascularspace involvement	7	2.2	8	5.3	0.071
Vaginal invasion	6	1.9	6	4.0	0.211
Ovarian metastasis	4	1.3	1	0.7	1.000
Uterine cavity invasion	10	3.1	3	2.0	0.764

No statistically significant difference for pathological result was found after neoadjuvant TP or CP chemotherapy. Abbreviations: TP, Taxanesplus platinum; CP, CPT-11plus platinum; *P < 0.05 indicates statistical significance.

ment regimes, and the clinical response of bidimensionally measurable and assessable disease was classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), which was the same rule that was adopted in our early research [14].

After completion of the safety follow-up (i.e., 28 days after surgery), the decision regarding systemic adjuvant therapy was at the discretion of the treating physician. Patients who had deep stromal invasion, parametrial extension, lymph vascular involvement, positive surgical margin or positive lymph nodes received postoperative irradiation or postoperative chemotherapy.

Follow-up study

DFS was defined as the time from the first day of assignment until the date of first relapse or death (regardless of cause). In the case of patients who were lost upon follow-up, DFS and OS data were censored at the time since the last follow-up that the patients were known to be alive.

Statistical analysis

The primary end point for this analysis was response and was analyzed on an intention-to-treat basis. The statistical methods used included the χ^2 test and Fisher's exact test for categorical variables. Two-sided Chi-squared and logistic regression analysis were used in the correlation between the baseline parameters and pathological response. The median follow-up time was calculated as the median observation time among all patients. Log-rank tests were used for the OS and DFS comparisons. A Cox proportional hazard model was used for multiple regression analysis to verify whether clinical variables and the pathological response variable predict OS and DFS. All *P*-values were two-tailed, and values < 0.05 were considered statistically significant. For survival comparisons, a log-rank model was used. All statistical analyses were carried out using the SPSS13.0 statistical software package.

Results

567 patients were recruited into the study (392 patients for the TP arm, and 175 patients for the CP arm), and 516 patients complete the treatment (354 patients in TP arm, and 162 patients in CP arm; Figure S1). Patient characters for both treatment groups are recorded in **Table 1**.

Short-term responses

Of the 354 patients in the TP arm, we observed 47 CRs (13.5%), 218 PRs (62.6%), 77 SDs (22.1%) and 6 PDs (1.7%), resulting in a clinical response rate of 76.1%. Of the 162 patients in the CP arm, we observed 20 CRs (12.6%), 104 PRs (65.4%), 28 SDs (17.6%) and 7 PDs (4.4%), resulting in a 78% clinical response rate. However, this difference was not statistically significant (P = 0.23; **Table 2**).

An OPT rate of the primary tumor was documented in 33 patients (9.3%) after the TP regime and in 16 patients (9.9%) after the CP regime (Table S1). Complete and optimal partial pathological responses (PCR and PR1) were achieved in 3.1% and 6.2% of patients for the TP arm and in 3.1% and 6.8% for the CP arm therapy, respectively. More details were depicted in Supplemental **Table 1**. A suboptimal pathological response was observed in 286 patients for the TP arm and in 134 patients for the CP arm (81.0% v 82.7%). 34 patients in the TP arm and 12 patients in the CP arm did not obtain surgery after treatment (9.6% v 7.4%). The differences in the pathological responses of the primary tumors between the two groups were not significant (P = 0.87; Table S2).

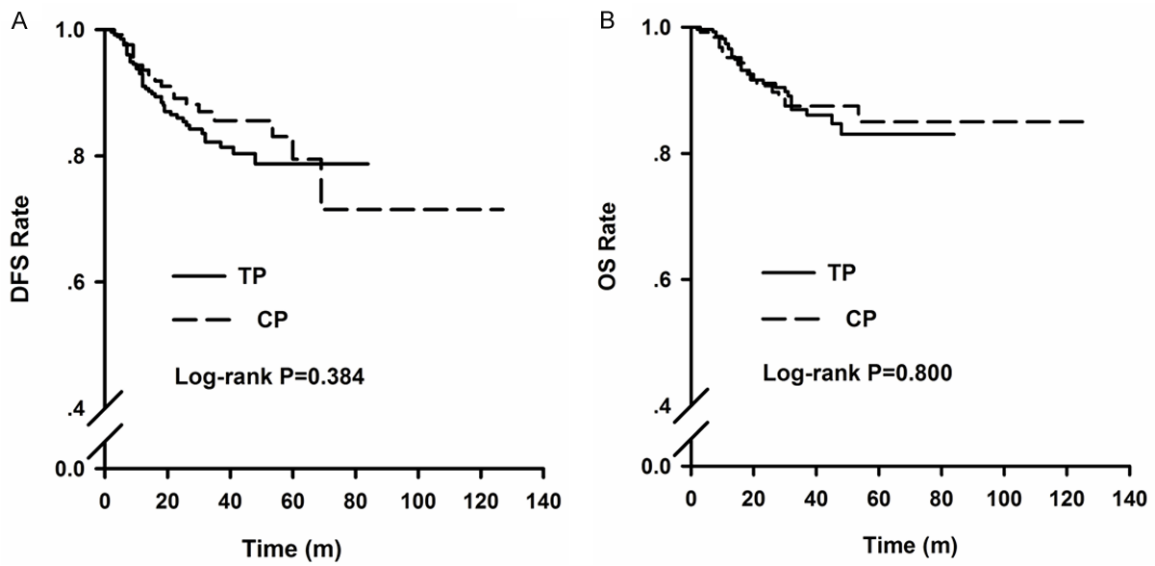

Figure 1. Kaplan-Meier analysis of DFS and OS in TP and CP arms. Comparing DFS rates between TP and CP arms using Log Rank test showed no statistically significant difference. Comparing OS rates between TP and CP arms using Log Rank test showed no statistically significant difference. $P < 0.05$ was considered to be significant.

Surgical results

Surgery was performed within 4 weeks of completing the last course of chemotherapy in 320 (90.4%) and 150 patients (92.6%) in the TP and CP arms, respectively. Node-positive disease was revealed in 64 patients in the TP arm versus 26 patients in the CP arm (20.1% *v* 17.4%, P = 0.49). Parametrial infiltration was revealed in 7 patients in the TP arm versus 5 patients in the CP arm (2.2% v 3.3%, P = 0.09). Vascular space involvement was observed in 7 and 8 of patients in the TP and CP arms, respectively (2.2% v 5.3%, P = 0.07), and vaginal invasion was observed in 6 and 6 patients in the TP and CP arms, respectively (1.9% v 4.0%, P = 0.21). Uterine cavity invasion was observed in one patient in the TP arm versus three patients in the CP arm (3.1% *v* 2.0%, P = 0.76), while ovarian metastasis was observed in 4 patients in the TP arm versus one patient in the CP arm (1.3% *v* 0.7%, P = 1.00) (**Table 3**).

Long-term responses: disease-free survival and overall survival

At a median follow-up period of 33 months (range, 2 to 127 months), 63 (15.7%) disease progressions were documented (44 in the TP arm and 19 in the CP arm). Thirty patients (10.9%) in the TP arm and 15 patients (12%) in the CP arm died; and the TP and CP arms had 82.2% and 85.6% DFS rates over 3 years, respectively. The 3-year OS rates were 87.0% in patients in the TP arm and 87.5% in patients in the CP arm, respectively. **Figure 1** depicts the log-rank test for the two regimen treatments. Comparison of the survival curves showed no statistically significant difference (P = 0.384 for DFS, P = 0.800 for OS). The CP regime showed higher DFS and OS for endophytic growth style with statistical difference (P = 0.013 for DFS, P = 0.027 for OS) as depicted by **Figure 2**. In **Figure 3**, we compared DFS and OS for different tumor grades. The CP regime showed higher DFS and OS for G2 tumor with statistical difference (P = 0.027 for DFS, P = 0.032 for OS). For G1 and G3 tumor grades, comparison of the survival curves showed no statistically significant difference.

Evaluation of independent prognostic factors for survival

A log-rank test was used to evaluate if the clinical response (CR + PR) was an independent prognostic factor for survival. Relative to patients in the clinical non-responder subgroup, the clinical responder subgroup demonstrated favorable DFS and OS rates ($P < 0.05$; **Figure 4A** and **4B**). In each arm, poorer outcomes were also observed in the clinical non-

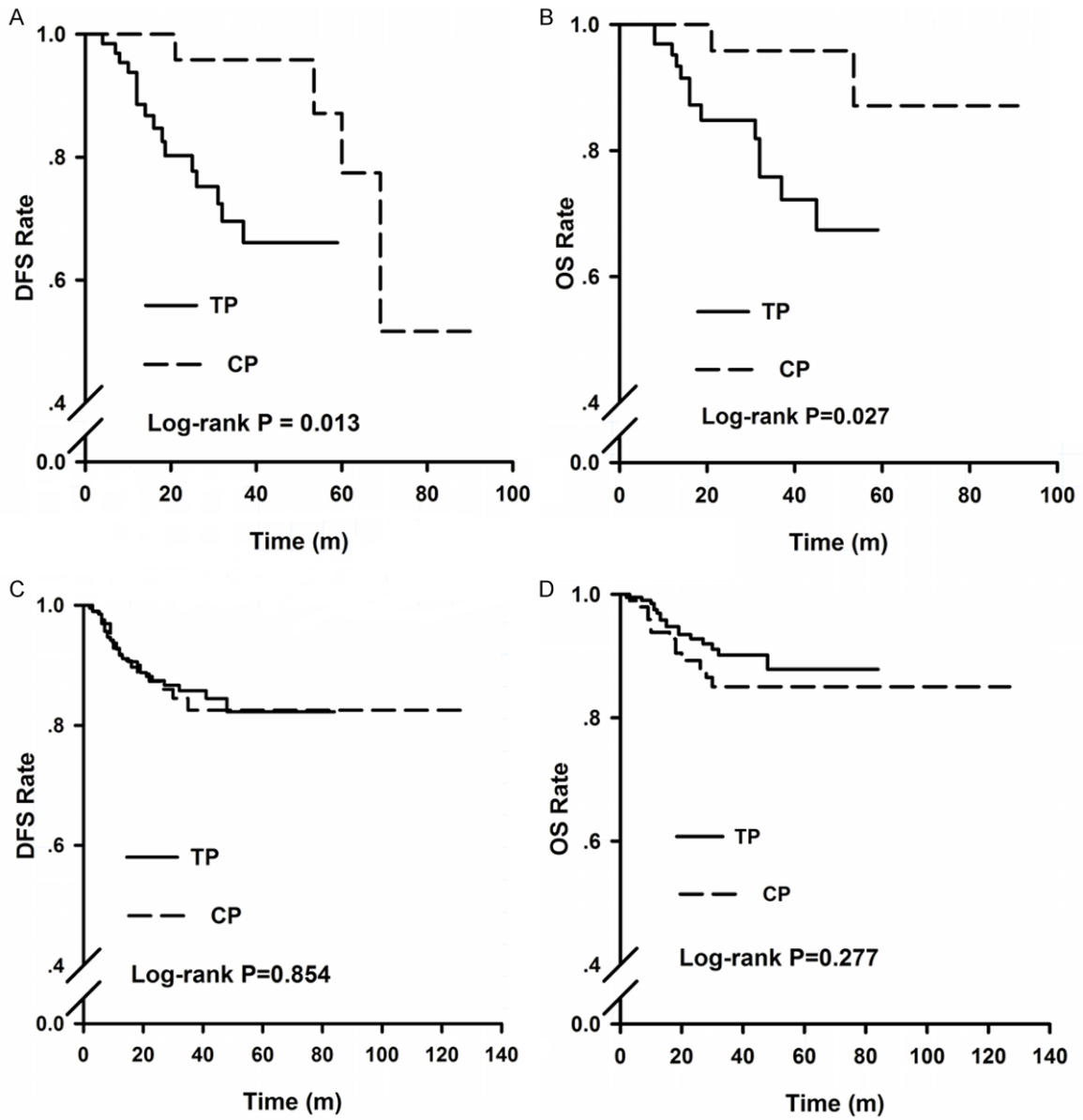

Figure 2. Kaplan-Meier analysis of DFS and OS in TP and CP arms stratified by growth style. Comparing DFS and OS rates between TP and CP arms using Log Rank test showed statistically significant difference in endophytic tumor style (A and B). Comparing DFS and OS rates between TP and CP arms using Log Rank test showed no statistically significant difference in exophytic tumor style (C and D). $P < 0.05$ was considered to be significant.

responder subgroup (**Figure 4C-F**). Then cox's regression model was used to assess prognostic factors for overall survival. We added factors such as clinical response and treatment arm to the model, together with variables including age, tumor size, growth style, tumor grade, FIGO stage and cell type. Data in **Table 4** showed that a non-response to NACT, older age (> 44 years), and a higher FIGO stage were independent prognostic risk factors for OS rate. Compared with the responder group, the HR attributing to the non-responder group was 2.68 (95% CI, 1.41 to 5.06; P = 0.002). Compared with the younger group, the average death rates were much greater in the older group (HR, 2.51; 95% CI, 1.23 to 5.14; P = 0.011). Relative to patients with FIGO stage Ibpatients, the average death rates were much greater in the FIGO stage IIb patients (HR, 2.84; 95% CI, 1.15 to 6.99; P = 0.023). Log-rank test

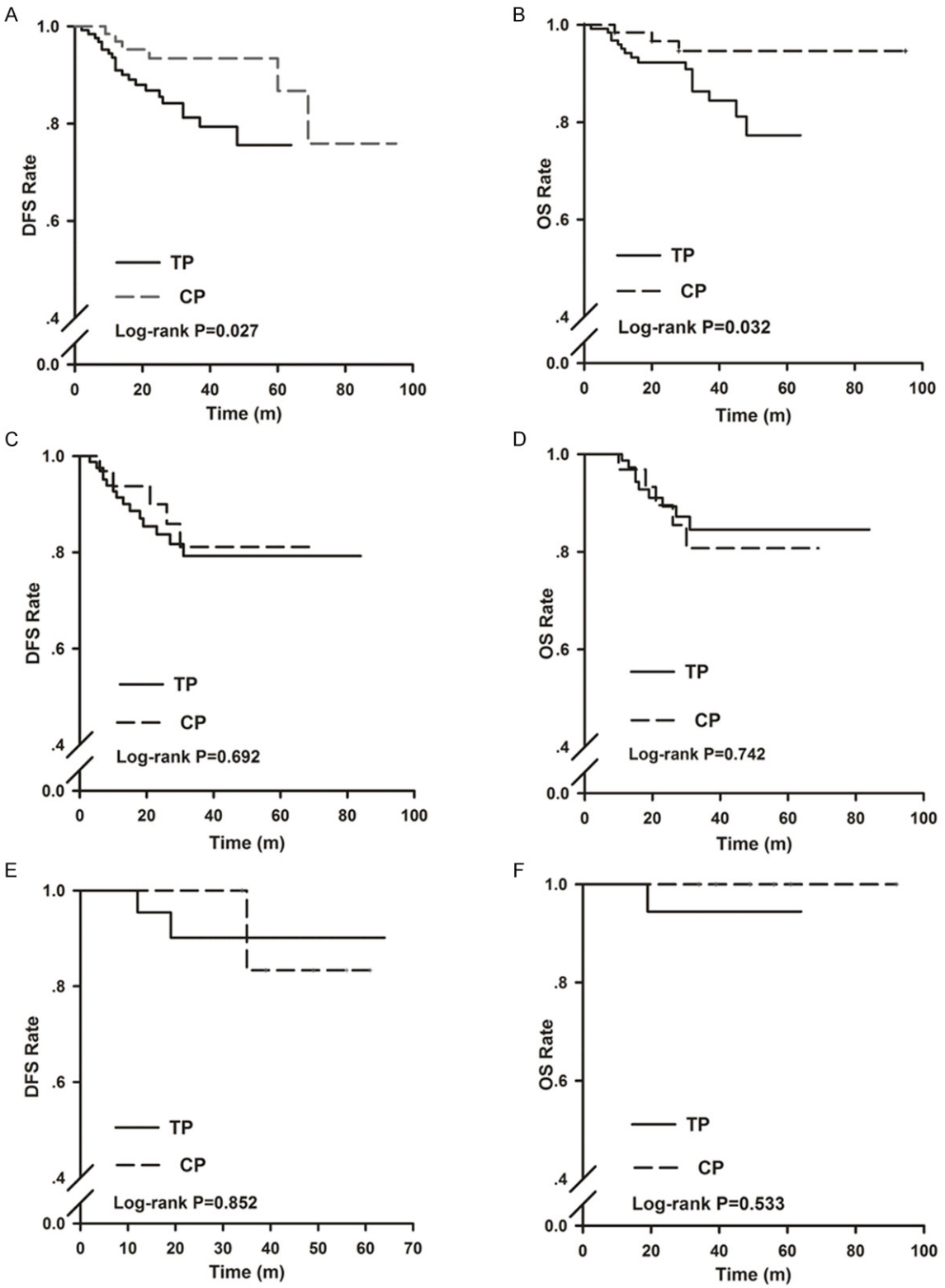

Figure 3. Kaplan-Meier analysis of DFS and OS in TP and CP arms stratified by tumor grade. Comparing DFS and OS rates between TP and CP arms using Log Rank test showed statistically significant difference in G2 (A and B) tumors. Comparing DFS and OS rates between TP and CP arms using Log Rank test showed no statistically significant difference in G1 (C and D) and G3 (E and F) tumors. $P < 0.05$ was considered to be significant.

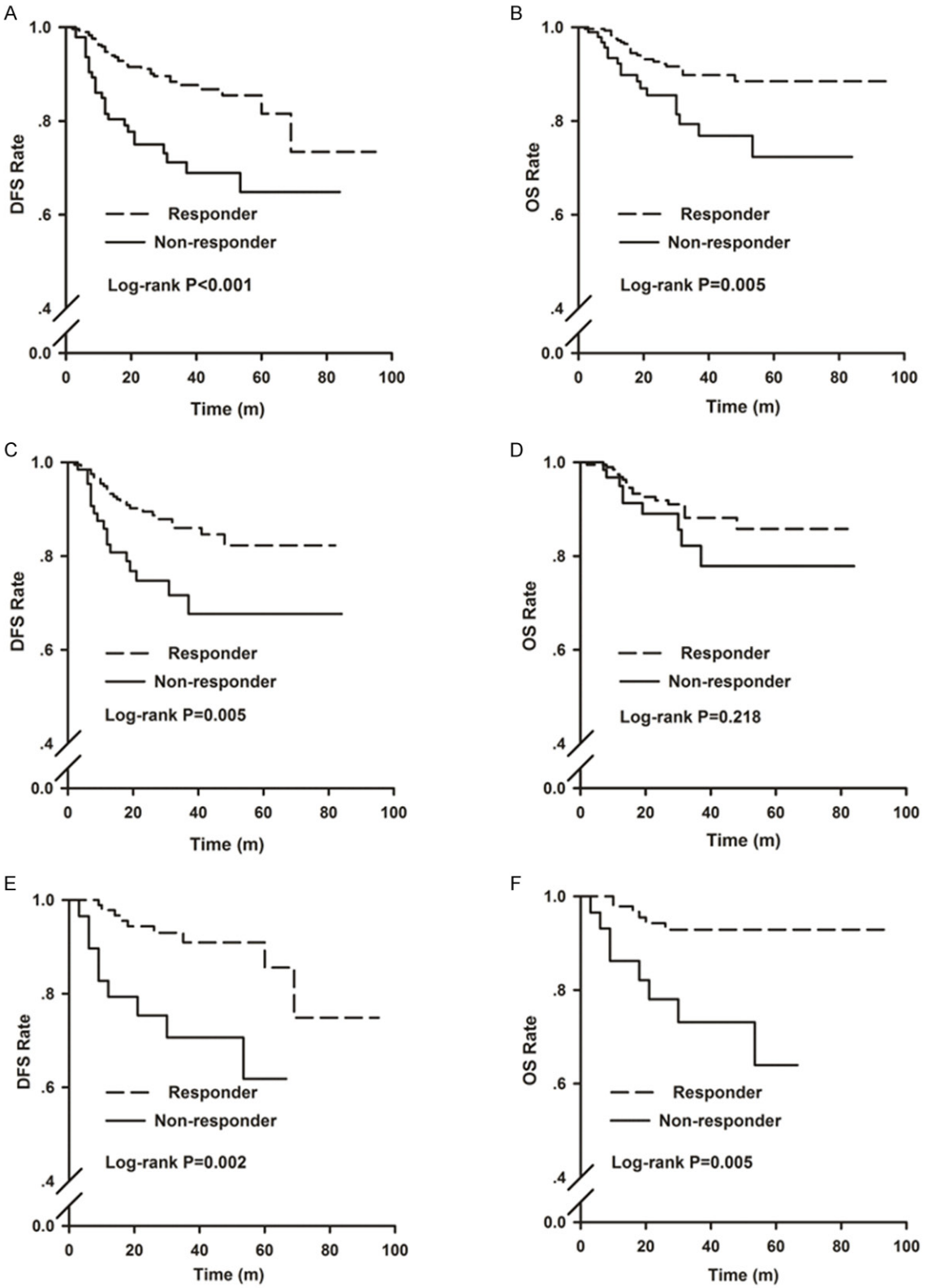

Figure 4. Kaplan-Meier analysis of DFS and OS stratified by clinical response. Comparing DFS and OS rates between responder and non-responder for both arms using Log Rank test showed statistically significant difference. Comparing DFS and OS rates between responder and non-responder using Log Rank test showed statistically significant difference in TP (C) and CP (E and F) tumors. DFS and OS rates between responder and non-responder showed statistically significant difference in all patients (A and B). OS rates in TP regimen was also in favor of responder although the difference was not significant (D). $P < 0.05$ was considered to be significant.

Table 4. Variables predictive of OS and DFS of all enrolled patients by multivariate Cox analysis using forward stepwise method

	OS		DFS	
	HR (95% CI)	P	HR (95% CI)	P*
Clinical response				
Responder	1		1	
Non-responder	2.68 [1.41, 5.06]	0.002	3.02 [1.77, 5.13]	0.000
Age				
Young group	1		1	
Old group	2.51 [1.23, 5.14]	0.011	2.56 [1.41, 4.66]	0.002
FIGO stage				
Ib	1		1	
IIa	1.01 [0.28, 3.67]	0.983	1.22 [0.47, 3.16]	0.678
IIb	2.84 [1.15, 6.99]	0.023	2.26 [1.10, 4.62]	0.026

*P < 0.05 indicates statistical significance.

for different age groups and FIGO stages also led to significant different survival rate (data not shown).

Toxicity

The treatment regimens were generally tolerable, and the rates of most adverse events were similar (Table S3). We recorded no toxicity-related deaths during treatment. Grade 3/4 nausea and vomiting was reported in 6.9% of patients in the TP group and in 12.0% of the CP group. Severe diarrhea was observed in 4 patients in the TP arm and in 9 patients in the CP arm (1.0% *v* 5.1%; P = 0.09). Celialgia occurred more frequently in the CP group, as severe celialgia (≥ Grade 3) occurred in 3 patients in the TP group, and in 2 patients in the CP group (0.8% *v* 1.1%, P = 0.65). Grade 3 to 4 anemia was reported in 26 and 17 of patients in the TP and CP treatment groups, respectively (6.6% *v* 9.7%, P = 0.20). Severe leukopenia was observed in 37 patients in the TP group and 13 patients in the CP group (9.4% *v* 7.4%, P = 0.44), while severe neutropenia was observed in 70 patients in the TP group and 40 patients in the CP group (17.9% v 22.9%, P = 0.02). Grade 3 to 4 thrombocytopenia was infrequent with 15 patients in the TP group and 11 patients in the CP group (3.8% *v* 6.3%, P = 0.20). With significant difference, severe liver enzyme (ALT) elevation was more likely to be induced by the TP regimen; 32 patients in the TP arm versus 5 patients in the CP arm showed this phenotype (8.2% v 2.9%, P = 0.02). Severe renal dysfunction was rare with only one patient in each arm, and it made no difference between the two groups.

Discussion

In the last decades, neoadjuvant chemotherapy has been applied as a new therapeutic approach of LACC because of unsatisfactory effects resulting from conventional therapy [15, 16]. Platinum is considered the single-most active cytotoxic agent and is always used in combination with other active agents, e.g. bleomycin, vinorelbine, taxanes, ifosfamide, irinotecan or gemcitabine [17-24]. Taxanes and irinotecan are considered among the most active drugs in adjuvant treatments because, when used as single agents or in combination with other drugs, they have proven effective in LACC [6-8, 10-12, 19]. Our study demonstrated that the CP regimen resulted in no significantly different OS rate compared with the TP regimen. To the best of our knowledge, this is the first study to compare the therapeutic effects between the two chemotherapy combinations of TP and CP.

The OPT rates were slightly higher among squamous cell type and post-menopausal women. Our research showed that the pCR and PR1 rates were 3.1% and 6.2% for the TP arm versus 3.1% and 6.8% for the CP arm, respectively. That is, the total optimal pathological response was similar between the TP arm and the CP arm, while a large proportion of patients acquired a sub-optimal response.

Our research showed that the complete and optimal (CR + PR) clinical response rates were 13.2% (13.5% in TP *v* 12.6% in CP) and 76.7% (76.1% in TP *v* 78.0% in CP), respectively. Patients with progressive disease were rare: only 6 women in the CP arm and 7 women in the TP arm. Sugiyama also conducted a phase II study of the CP regimen, which showed a progressive disease rate of 4-10%, which was similar to the findings in our research [7, 8]. The number of patients who underwent radical surgery was 319 (90.4%) and 150 (92.6%) in the TP and CP regimen groups, respectively. The percentage of patients with a pathologically negative pelvic nodal status after surgery was slightly higher after CP compared with TP treat-

ment, but these values were not significantly different. These findings also reflected the similar systemic efficacy of the two regimens. Thirty-four patients in the TP arm and 12 patients in the CP arm underwent radio therapy instead of surgery because sufficient improvement had not been achieved.

The treatment regimens were generally well tolerated, and no deaths occurred as a result of toxicity in the TP arm and in the CP arm. The predominant side effects were myelosuppression in both groups. Although most patients experienced blood cell count decline, severe (Grade 3 to 4) temporary or persistent hematologic toxicity was uncommon (anemia, 7.6%; leukopenia, 8.8%; neutropenia, 19.4%; thrombocytopenia, 4.6%). Similarly, mild (Grade 1 to 2) nausea/vomiting occurred frequently, with severe events observed in only 8.5% of patients. Between the two treatment arms, severe (Grade 3 to 4) celialgia and diarrhea were more likely to be induced by the CP arm ($P = 0.65$, and $P = 0.002$), with more frequent severe elevation of transaminases induced by TP ($P = 0.02$). Long also showed similar occurrence rates in a sub-treatment group of the TP regime [11]. Renal toxicity was rare in both arms.

The estimated value for progression-free survival at 3 years was 83.3% (82.2% in patients receiving the TP regimen, and 85.6% in patients receiving the CP regimen). The overall survival at 3 years was 87.2% (87.0% in patients receiving the TP regimen, and 87.5% in patients receiving the CP regimen). Comparison of disease-free survival and overall survival curves showed no statistically significant difference, with $P = 0.38$ for DFS and $P = 0.80$ for OS. Although long demonstrated a significant advantage in survival due to combined regimens compared with single cisplatin treatment, i.e. single agent cisplatin v cisplatin and topotecan, in patients with advanced cervical cancer [11]. We found no evidence of a difference in survival rate in favor of either arm. Whether the CP regimen had superiority over the TP regimen in OS must be further explored in a larger population and over a longer follow-up period.

Three variables including clinical response, age and FIGO stage were demonstrated as independent prognostic factors in our study both for DFS and OS. Our last retrospective study also manifested that clinical responder group processed a superior long term survival rate, compared with primary surgery group and non-responder group. This cohort study validated our previous finding, as both the researches showed that the achievement of clinical response after neoadjuvant chemotherapy was a significant prognostic factor for survival. So clinical response should be treated as a surrogate end point for predicting long term survival in NACT cervical cancer patients. And it can be used to more quickly evaluate the efficacy of a new treatment. For example, the difference in response could be regarded as an early indicator of a treatment difference in correlation with survival.

In conclusion, we found the regime CPT-11plus platinum (CP) has comparable effect with the taxanes plus platinum (TP) regime. The CP regime showed higher survival rate for endophytic growth style and also for G2 tumor. Three factors including clinical response, age and FIGO stage were identified as independent prognostic risk factors for DFS and OS. However, our research has some limitations. The follow up time, with a mean value of 33 months, was not long enough because a portion of the patients were gathered as recently as one or two years. A longer follow up time is appropriate to determine which regime translates into an advantage in overall survival. A prospective, randomized study with a longer follow-up period may be necessary to determine which regime is a more suitable treatment.

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Disclosure of conflict of interest

None.

Abbreviations

TP, Taxanesplus platinum; CP, CPT-11plus platinum; LACC, Locally advanced cervical cancer; NACT, Neoadjuvant chemotherapy; FIGO, International Federation of Gynecology and Obste-

trics; DFS, Disease-free survival; OS, Overall survival; pCR, Pathological complete response; OPT, Optimal pathologic response.

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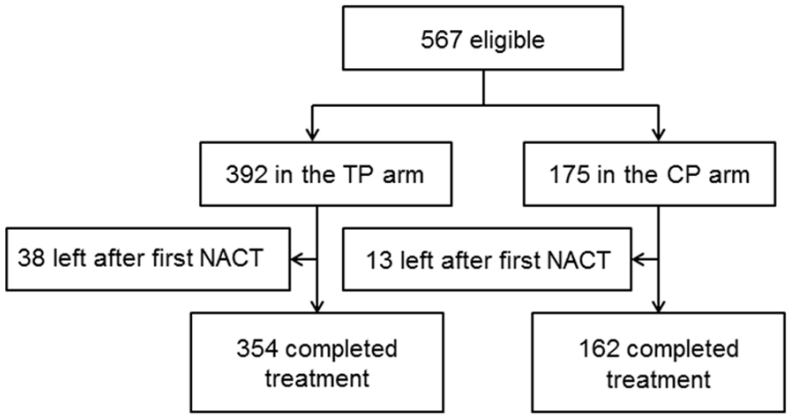

Figure S1. Diagram of patients. 567 patients were recruited into the study (392 patients for the TP arm, and 175 patients for the CP arm), and 516 patients complete the treatment (354 patients in TP arm, and 162 patients in CP arm).

Table S1. Optimal pathological response to neoadjuvant TP or CP chemotherapy

Response	TP arm (n = 354)		CP arm (n = 162)		*P*
	No.	%	No.	%	
					0.871
OPT-PCR	11	3.1	5	3.1	
OPT-PR1	22	6.2	11	6.8	
Sub-OPT	286	81.0	134	82.7	
No surgery	34	9.6	12	7.4	
Missing	1				

P < 0.05 indicates statistical significance.

Table S2. Stratification of patient and tumor characteristics by optimal pathologic response to neoadjuvant TP or CP chemotherapy: number and percentage of patients

	TP arm (n = 318) Pathologic Response				CP arm (n = 150) Pathologic Response				P
	OPT		Non-OPT		OPT		Non-OPT		
	No.	%	No.	%	No.	%	No.	%	
All patients	33	10.4	285	89.6	16	10.7	134	89.3	0.924
Age, years									
< 44	16	11.8	120	88.2	4	6.0	63	94.0	0.193
≥ 44	17	9.3	165	90.7	12	14.5	71	85.5	0.216
Tumor size, cm									
< 4	16	13.4	103	86.6	6	10.3	52	89.7	0.557
≥ 4	13	7.2	167	92.8	10	11.8	75	88.2	0.220
Unknown	4		15		0		7		
Growth style									
Endophytic	12	15.6	65	84.4	3	9.4	29	90.6	0.391
Exophytic	21	8.9	216	91.1	13	11.2	103	88.8	0.483
Unknown	0		4		0		2		
Tumor grade									
G1	3	11.5	23	88.5	1	10.0	9	90.0	0.895
G2	11	7.0	146	93.0	5	6.9	67	93.1	0.986
G3	6	5.7	99	94.3	6	10.5	51	89.5	0.264
Unknown	13		17		4		7		
FIGO stage									
Ib	10	10.6	84	89.4	6	11.5	46	88.5	0.868
IIa	8	11.4	62	88.6	4	9.8	37	90.2	0.784
IIb	15	9.7	139	90.3	6	10.5	51	89.5	0.866
Cell type									
Squamous	32	11.7	242	88.3	15	11.1	120	88.9	0.866
Non-squamous	1	2.4	41	97.6	0	0	14	100.0	0.560
Unknown	0		2		1		0		
Menopausal status									
Postmenopausal	8	11.3	63	88.7	10	31.3	22	68.8	0.013
Premenopausal	24	9.8	221	90.2	6	5.4	105	94.6	0.167
Unknown	1		1		0		7		

Comparation for optimal pathologic response to neoadjuvant TP or CP chemotherapy stratified by patient characteristics. The response rates were nearly the same in most stratifications. $P < 0.05$ indicates statistical significance.

Table S3. Serious adverse events after neoadjuvant TP or CP chemotherapy

Adverse Event	All (n = 567)		TP (n = 392)		CP (n = 175)		P*
	No.	%	No.	%	No.	%	
Nausea/Vomiting	48	8.5	27	6.9	21	12.0	0.04
Diarrhea	13	2.3	4	1.0	9	5.1	0.002
Celialgia	5	0.9	3	0.8	2	1.1	0.65
Anemia	43	7.6	26	6.6	17	9.7	0.20
Leukopenia	50	8.8	37	9.4	13	7.4	0.44
Neutropenia	110	19.4	70	17.9	40	22.9	0.16
Thrombocytopenia	26	4.6	15	3.8	11	6.3	0.20
Liver enzymes (ALT)	37	6.5	32	8.2	5	2.9	0.02
Renal	2	0.4	1	0.3	1	0.6	0.52

Most serious adverse events after neoadjuvant TP or CP chemotherapy were similar while severe neutropenia was more likely to be induced by the CP regimen. *$P < 0.05$ indicates statistical significance.