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ORIGINAL ARTICLE

Prognostic factors from a randomized phase III trial of paclitaxel and carboplatin versus paclitaxel and cisplatin in metastatic or recurrent cervical cancer: Japan Clinical Oncology Group (JCOG) trial: JCOG0505-S1

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Abstract
Purpose The Japan Clinical Oncology Group (JCOG) trial JCOG0505 demonstrated the statistically significant non-inferiority of paclitaxel plus carboplatin (TC) to paclitaxel plus cisplatin (TP) in terms of overall survival (OS) in metastatic or recurrent cervical cancer. In that trial, patients were randomly assigned, adjusting for institution and known prognostic factors. The objective of this ancillary study was to evaluate the appropriateness of the adjustment factors used to have randomly assigned treatments and to investigate new potentially useful prognostic factors of paclitaxel plus platinum for future randomized trials in metastatic or recurrent cervical cancer.
Methods The study subjects comprised 244 eligible patients in the JCOG0505 who were merged to have received either TC or TP. The effects of the following factors on OS were investigated using a Cox regression model taking into consideration the adjustment factors used in randomization in this trial (e.g., performance status [PS]) and other baseline factors, including platinum-free interval (PFI), pretreatment hemoglobin levels (PHLs), and pretreatment platelet counts (PPCs).
Results The median follow-up was 17.6 months, and median OS was 18.0 months. The hazard ratio was 1.83 in patients with a PS of 1 or 2 (vs. 0; $P = 0.0004$; 95 % confidence interval [CI] 1.31–2.55), 2.92 in patients with a PFI of <6 months (vs. PFI of ≥12 months; $P < 0.0001$; 95 % CI 1.73–4.91), 2.09 in patients with a PFI of <12 months (vs. PFI of ≥12 months; $P = 0.0034$; 95 % CI 1.28–3.44), and 0.69 in patients with PHL higher than or equal to the median value (vs. less than the median; $P = 0.016$; 95 % CI 0.51–0.93). No significant differences were obtained for PPC or the other known factors.
Conclusions In addition to the known prognostic factor of PS, which was used as an adjusting factor, a PFI of <12 months and lower PHL were newly demonstrated to be associated with poor outcomes in patients with metastatic or recurrent cervical cancer. These new prognostic factors should be validated in future prospective trials.
Clinical trial information UMIN-CTR[http://www.umin.ac.jp/ctr/] ID: C000000335.

Keywords Cervical cancer · Metastatic · Recurrent · Platinum-free interval · Pretreatment hemoglobin level

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Introduction

Previous studies have reported that age [1], performance status (PS) [1–3], time to recurrence, and site of recurrence [1–5] are predictors of response to chemotherapy in women with advanced or recurrent cervical cancer for which local treatment is not indicated. As for the site of recurrence, intrapelvic recurrence has been linked to a particularly poor prognosis [1–5], and recurrence in a previously irradiated field has been associated with a poor response to subsequent chemotherapy.

Previous treatment with cisplatin and progression-free survival after treatment with cisplatin (platinum-free interval) has also been reported to affect the response to chemotherapy after recurrence [6]. Many patients with recurrence have advanced disease at initial treatment and have received cisplatin-based chemoradiotherapy as initial therapy. In clinical trials performed by the Gynecologic Oncology Group (GOG), an increased proportion of patients who had previously received chemoradiotherapy was associated with a decreased proportion of patients who responded to cisplatin monotherapy as treatment for recurrence [7]. These findings indicate that patients with recurrence who have a history of treatment with cisplatin are likely to have a poorer response to cisplatin as treatment for recurrence [3, 5, 8, 9]. The results of the GOG179 trial suggested that platinum-free interval (PFI) is a prognostic factor [7]. Retrospective studies in Japan have also demonstrated that PFI is a predictor of poor outcomes in patients with recurrence [10, 11].

Anemia and thrombocytosis at diagnosis have been reported to be poor prognostic factors for various malignancies, including cervical cancer [12–18]. Anemia and hypoxia may lead to enhanced angiogenesis, increased tumor-cell proliferation, increased metastatic potential, decreased cell response to apoptosis signals, and resistance to therapy [19]. Thrombocytosis probably also reflects a cascade of biological events correlated with tumor aggressiveness [14, 20, 21].

The Japan Clinical Oncology Group (JCOG) trial JCOG0505 demonstrated the statistically significant non-inferiority of paclitaxel plus carboplatin (TC) to paclitaxel plus cisplatin (TP) in terms of overall survival (OS) in patients with metastatic or recurrent cervical cancer [6]. In that trial, patients with incurable disease (including patients with previous therapy up to one regimen of platinum-based chemotherapy) were randomly assigned to treatment with the minimization method, adjusting for institution and known prognostic factors such as PS, histologic type, and the history of radiotherapy (RT). The objective of this ancillary study was to evaluate the appropriateness of the adjustment factors used to randomly assign treatments in the JCOG0505 and to explore new prognostic factors on the basis of the trial results, thereby contributing to the planning of future studies in same population.

Patients and methods

Patients population

The design and methods of JCOG0505 were reported previously [6]. Briefly, this phase III trial was designed to confirm the non-inferiority of TC to TP in terms of OS and to evaluate other clinical benefits of TC in patients who had stage IVB, persistent or recurrent cervical cancer with a histologic diagnosis of squamous cell carcinoma (SCC) or non-squamous cell carcinoma (non-SCC). Randomization was performed centrally in a 1:1 ratio at the JCOG Data Center with the use of a minimization method to adjust for institution, Eastern Cooperative Oncology Group (ECOG) PS (0–1 or 2), tumor histology (SCC or non-SCC), and the presence of tumors outside of the previously irradiated field (yes or no). Both regimens were repeated every 21 days for a maximum of six cycles until disease progression or unacceptable toxicity. Eligible patients had primary stage IVB disease or a first or second recurrence of disease, with at least one metastatic lesion beyond the pelvic cavity, or at least one localized lesion inside the previously irradiated field. In addition, patients were permitted to have received no more than one prior regimen of platinum-based chemotherapy, including concurrent chemoradiotherapy, with no prior taxane chemotherapy.

Of the 244 eligible patients in the JCOG0505 who were assigned to receive either TC or TP, one patient was excluded from analysis because of missing covariate data. The effects of the following factors on OS were evaluated: pretreatment hemoglobin levels (median 11.8 g/dL: higher than or equal to vs. less than the median value), pretreatment platelet counts (median $27.15 \times 10^4/mm^3$: higher than or equal to vs. less than the median value), and the adjustment factors used for randomization in the JCOG0505, which included PS (0 vs. 1 or 2), histologic type: SCC vs. non-SCC, and history of RT: (prior RT for all recurrent lesions vs. no RT or at least one lesion without RT).

Statistical analysis

The effects of these factors were investigated using a univariate and multivariate Cox regression model taking into consideration the adjustment factors used for randomization (PS, histologic type, and history of RT) and other baseline factors, such as age ($\leq$50 vs. $\geq$51); disease stage (stage IVB vs. recurrent vs. re-recurrent); lesion site (A: at least one metastatic lesions outside the pelvic cavity except in the para-aortic lymph nodes (LN) and/or inguinal LN vs.

B: no metastatic lesion outside the pelvic cavity except in the para-aortic LN and/or inguinal LN, and at least one of these lesions has been irradiated vs. C: all lesions are localized inside the pelvic cavity, and at least one of them has been irradiated); PFI: (no history of treatment with platinum compounds vs. <6 months vs. ≥6 and <12 months vs. ≥12 months); and complications before treatment: (yes vs. no).

OS was estimated with the use of the Kaplan–Meier method [22]. A Cox proportional hazards model was used to estimate hazard ratios [23]. Hazard ratios indicating the effects of prognostic factors on the risk of death were calculated. All analyses were carried out using SAS release 9.1 (SAS Institute, Cary, NC, USA).

Results

Study schema

Figure 1 shows the study schema. Two hundred and fifty-three patients were enrolled and randomized. Nine patients were ineligible. Data on 244 eligible patients were analyzed.

Patient characteristics

Patient characteristics are listed in Table 1. Most patients had an ECOG PS of 0 or 1, and 83 % of the patients had a histologic diagnosis of SCC. The patient characteristics, including disease status, tumors outside the previously irradiated field, and complications before treatment, were similar to those reported previously. Thirteen percentage of the patients had a PFI of <6 months, 16 % had a PFI of ≥6 months to <12 months, 23 % had a PFI of ≥12 months, and 48 % had received no platinum therapy.

Effects on OS as evaluated with a univariate and multivariate Cox regression model

Table 2 shows the results of analysis with a univariate and multivariate Cox regression model. Univariate analysis demonstrated that a PS of 1–2 (vs. 0) and an age of ≥51 years (vs. ≤50 years) were significantly associated with OS ($P = 0.0001$; hazard ratio, 1.84; 95 % CI 1.34–2.51 and $P = 0.02$, hazard ratio, 0.72; 95 % CI 0.55–0.95, respectively). In contrast, histologic type, a history of radiotherapy, disease status, lesion site, and complications had no effect on survival. In addition, the hazard ratio was 1.65 in patients with no history of treatment with platinum compounds (vs. PFI of ≥12 months; $P = 0.01$; 95 % CI 1.13–2.41), 3.06 in patients with a PFI of <6 months (vs. PFI of ≥12 months; $P < 0.0001$; 95 % CI 1.88–4.99), 2.12

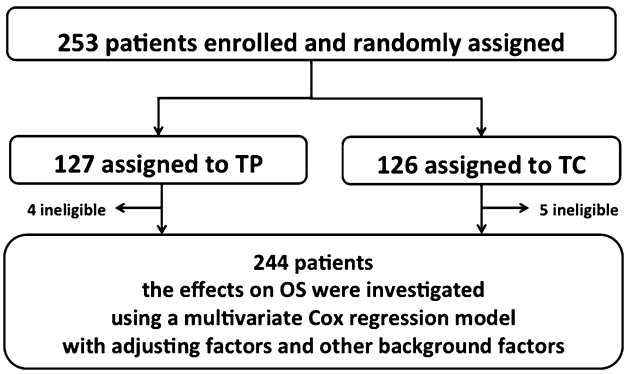

Fig. 1 Study schema

Table 1 Patient characteristics

Characteristic	No. of patients (%)
Age	
≤50 years	104 (42.6)
≥51 years	140 (57.4)
Performance status (ECOG)	
0	185 (75.8)
1	54 (22.1)
2	5 (2.0)
Tumor histology	
Squamous cell carcinoma	202 (82.8)
Adenosquamous	7 (2.9)
Adenocarcinoma	35 (14.3)
Disease status	
IVB or persistent	51 (20.9)
First recurrent	161 (66.0)
Second recurrent	32 (13.1)
Tumors outside prior irradiation field	
Yes	152 (62.3)
No	92 (37.7)
Complications before treatment	
Yes	37 (15.2)
No	207 (84.8)
Platinum-free interval	
None	117 (48.0)
<6 months	32 (13.1)
≥6 and <12 months	40 (16.4)
≥12 months	55 (22.5)
Pretreatment hemoglobin levels[a]	
<11.8 g/dL	121 (49.8)
≥11.8 g/dL	122 (50.2)
Pretreatment platelet counts	
$<27.15 \times 10^4/mm^3$	122 (50)
$\geq 27.15 \times 10^4/mm^3$	122 (50)

[a] One patient was excluded from this analysis due to missing of pretreatment hemoglobin level data

Table 2 Effects on OS by Cox regression model

Factor	Univariate analysis			Multivariate analysis[a]		
	HR	95 % CI	*P* value	HR	95 % CI	*P* value
PS 1 or 2 (vs. PS 0)	1.84	1.34–2.51	0.0001	1.83	1.31–2.55	0.0004
Squamous cell (vs. non-squamous cell)	1.14	0.79–1.64	0.49	1.04	0.71–1.51	0.84
Tumors outside prior irradiation field: no (vs. yes)	0.88	0.66–1.18	0.39	0.77	0.50–1.19	0.25
Age: ≥51 years (vs. ≤50 years)	0.72	0.55–0.95	0.02	0.81	0.61–1.08	0.16
Disease status						
First recurrent (vs. stage IVB)	0.88	0.63–1.23	0.45	0.97	0.62–1.50	0.88
Second recurrent (vs. stage IVB)	0.74	0.45–1.21	0.23	0.88	0.51–1.53	0.66
Lesion site						
B (vs. A)	0.62	0.37–1.03	0.064	0.74	0.42–1.28	0.28
C (vs. A)	1.11	0.80–1.54	0.54	1.36	0.83–2.24	0.23
Complications before treatment: yes (vs. no)	1.19	0.82–1.73	0.36	1.03	0.69–1.55	0.88
Platinum-free interval						
No history of treatment (vs. ≥12 months)	1.65	1.13–2.41	0.01	1.31	0.85–2.02	0.22
< 6 months (vs. ≥12 months)	3.06	1.88–4.99	<0.0001	2.92	1.73–4.91	<0.0001
≥6 and <12 months (vs. ≥12 months)	2.12	1.33–3.38	0.002	2.09	1.28–3.43	0.0034
Pretreatment hemoglobin levels[a]						
≥11.8 g/dL (vs. < 11.8 g/dL)	0.60	0.46–0.79	0.0003	0.69	0.51–0.93	0.016
Pretreatment platelet counts						
$\geq 27.15 \times 10^4/mm^3$ (vs. $<27.15 \times 10^4/mm^3$)	1.31	0.99–1.72	0.058	1.31	0.98–1.76	0.071

Lesion site A: at least one metastatic lesion outside the pelvic cavity except in the para-aortic lymph nodes [LN] and/or inguinal LN

Lesion site B: no metastatic lesion outside the pelvic cavity except in the para-aortic LN and/or inguinal LN, and at least one of these lesions has been irradiated

Lesion site C: all lesions are localized inside the pelvic cavity, and at least one of them has been irradiated

[a] One patient was excluded from this analysis for pretreatment hemoglobin levels and multivariate analysis due to missing of pretreatment hemoglobin level data

in patients with a PFI of ≥6 and <12 months (vs. PFI of ≥12 months; $P = 0.0002$; 95 % CI 1.33–3.38), and 0.60 in patients with pretreatment hemoglobin levels higher than or equal to the median value (vs. less than median; $P = 0.0003$; 95 % CI 0.46–0.79). On the other hand, OS was not significantly related to the pretreatment platelet count or other factors.

Multivariate analysis demonstrated that a PS of 1–2 (vs. 0) was significantly associated with OS ($P = 0.0004$; hazard ratio: 1.83; 95 % CI 1.31–2.56). In contrast, histologic type, history of radiotherapy, age, disease status, lesion site, and complications had no effect on survival. In addition, the hazard ratio was 2.92 in patients with a PFI of <6 months (vs. PFI of ≥12 months; $P < 0.0001$; 95 % CI 1.73–4.91), 2.09 in patients with a PFI of ≥6 and <12 months (vs. PFI of ≥12 months; $P = 0.003$; 95 % CI 1.28–3.43), and 0.69 in patients with pretreatment hemoglobin levels higher than or equal to the median value (vs. less than median; $P = 0.016$; 95 % CI 0.51–0.93). On the other hand, OS was not significantly related to the pretreatment platelet count or other factors.

Discussion

Metastatic and recurrent cervical cancer is a difficult clinical entity to be treated because of its poor outcomes, with a reported 1-year survival between 15 and 20 % [24]. Chemotherapy is the main treatment for this subgroup of patients, excluding those in whom long-term survival can be achieved by surgery or radiotherapy. Despite substantial efforts to improve survival in the past decades, the role of chemotherapy in this subset of patients remains palliative [9].

Prognostic factors in patients with recurrent cervical cancer have been investigated in several studies, which found that recurrence within the previously irradiated field, young age, poor PS, and a short time to progression from the initial diagnosis are significant predictors of shorter survival [25, 26].

The JCOG0505 showed no trend, suggesting that tumor histology or the presence of tumors outside of the previously irradiated field was a prognostic factor for OS [1, 4]. The results of our study suggested that tumor histology or

the presence of tumors outside of the previously irradiated field might not have to be included as adjustment factors for the random allocation of treatments in subsequent clinical trials.

On the other hand, our results demonstrated a strong correlation between OS and PFI. In recent phase III trials as well, prior concurrent chemoradiotherapy has been linked to an increased risk of death [7, 27], and recent studies have reported that PFI is a predictor of response to second-line platinum-based chemotherapy and a prognostic factor in advanced or recurrent cervical cancer [10, 11]. The cutoff of PFI varies among reports. Our study showed that PFI less than 12 months was a prognostic factor. The effectiveness of platinum-based chemotherapy has been reported to be higher in patients with cervical cancer who had relapse more than 2 years after receiving platinum-based chemotherapy than in those who had relapse within 6 months after receiving such chemotherapy [9]. Tanioka et al. [10] reported that a PFI of less than 12 months was a stronger predictor of outcomes. Matoda et al. [11] showed that only a long PFI of more than 24 months was a prognostic indicator of the response to rechallenge with a platinum-based regimen in advanced and recurrent cervical cancer. Although the cutoff value of PFI is different, our findings indicating PFI less than 12 months as a prognostic factor were compatible with these previous findings.

The present study also showed that the pretreatment low hemoglobin level was a poor prognostic factor ($P = 0.016$; hazard ratio: 0.69; 95 % CI 0.51–0.93). On the other hand, the pretreatment platelet count tended to be associated with survival, but was not a statistically significant prognostic factor ($P = 0.071$; hazard ratio: 1.31; 95 % CI 0.98–1.76). It has been controversial whether pretreatment hemoglobin levels and platelet counts have prognostic significance in this clinical setting. Most cancer patients have anemia, mainly due to iron metabolism disorders, endogenous erythropoietin deficiency, suppression of erythroid progenitor cells by tumor-released cytokines, and blood loss [28].

In cervical cancer, few studies have evaluated the prognostic relevance of hemoglobin levels in patients who received neoadjuvant chemotherapy and radical hysterectomy, and consistent results have yet to be obtained [17, 19]. However, it has been reported that anemia negatively affects the clinical outcomes of patients who received radiotherapy [15, 18] or chemoradiotherapy [16]. This study also showed that anemia is a poor prognostic factor in the setting of chemotherapy alone for metastatic or recurrent cervical cancer patients. On the other hand, the pretreatment platelet count has been found to be an independent predictor of survival in some series of patients with cervical cancer [12, 14], but not in others [13].

Malignant cells often produce cytokines and growth factors enabling megakaryopoiesis induction [29], and platelets, in turn, can secrete growth factors that stimulate cancer-cell proliferation, angiogenesis, and distant progression [20, 21, 30]. Platelets are a rich source of both platelet-derived growth factor, which is a potent mitogen, and thrombospondin, which supports the adhesion of tumor cells to the endothelium by increasing expression of urokinase-type plasminogen activator [20, 21]. Thus, pretreatment platelet count can be a prognostic factor, since thrombocytosis reflects a cascade of biological events correlated with tumor aggressiveness. The unclear prognostic relevance of the pretreatment platelet count may be attributed in part to the heterogeneity of patient populations and treatment modalities.

To our knowledge, this is the largest study of prognostic factors in terms of the number of subjects with metastatic or recurrent cervical cancer who received the same class of chemotherapy. The use of the known prognostic factors of histologic type and the presence or absence of non-irradiated lesions as adjustment factors had no significant effect on the results of multivariate analysis. In addition to the known prognostic factor of PS, a PFI of less than 12 months and lower pretreatment hemoglobin level were shown to be significant poor prognostic factors on univariate and multivariate analysis. On the other hand, pretreatment platelet counts tended to be slightly, but not significantly related to outcomes. No other factors were significantly related to outcomes.

In conclusion, newly found prognostic factors, PFI of less than 12 months and lower pretreatment hemoglobin level, are considered as new adjustment factors in future clinical trials.

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Compliance with ethical standards

Conflict of interest The authors have declared no conflict of interest.

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