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ORIGINAL ARTICLE

Second platinum therapy in patients with uterine cervical cancer previously treated with platinum chemotherapy

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Abstract
Background After the front-line platinum-based regimens including concurrent chemoradiotherapy (CCRT) in patients with advanced or recurrent cervical cancer, platinum-based regimens are often used again.
Patients and methods We retrospectively studied the predictors of response to second platinum therapy and prognostic factors of survival of 65 women who had received ≥2 platinum-based regimens in order to evaluate the effects of platinum-free interval (PFI), i.e., the interval between the platinum therapies.
Results The median survival and PFI were 11.0 and 11.1 months, respectively. The response rate was 42% overall and 36% in the 36 patients who had received CCRT. The response rate increased in parallel with the length of the PFI. Multivariate analyses showed a PFI for ≥12 months (odds ratio [OR] = 0.20), a PS of 0 (OR = 0.16) and a maximum tumor diameter ≤30 mm (OR = 0.18) were predictive of response. Multivariate analyses also revealed a PFI for ≥6 months (hazard ratio [HR] = 0.44) and a PS of 0 (HR = 0.30) were prognostic of survival.
Conclusion Our exploratory study demonstrated that PFI has both predictive and prognostic value for second platinum therapy in patients with advanced or recurrent cervical cancer.

Keywords Cervical cancer · Platinum-free interval · Second line · Prognostic · Predictive

Introduction

Cervical cancer is a major cause of death among women. In 2002, there were estimated to be 493,243 cases and 273,505 associated deaths worldwide [1]. Despite improvements in concurrent chemoradiotherapy (CCRT), patients with recurrence or metastasis have poor prognosis, with a 1-year survival rate between 15 and 20% [2].

Chemotherapy for advanced or recurrent cervical cancer has been used mainly to palliate symptoms and improve response rate, while maintaining an acceptable level of toxicity. Single-agent cisplatin has been the standard first-line treatment since 1981, when a response rate of 38% was reported [3]. Carboplatin has had response rate of 15–28% [4, 5]. On the other hand, second-line chemotherapy after the front-line regimens including CCRT remains controversial. Single agents such as paclitaxel [6], irinotecan [7] and ifosfamide [8] were found to be clinically active; however, none of these agents have became the standard therapy after platinum-based regimens because of lower response rates and lack of data from phase III trials. It therefore seems reasonable to administer platinum-based chemotherapy again to selected patients who previously received such therapy. However, the optimal clinical

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conditions for rechallenge with second platinum therapy are unclear.

We studied the effects of the platinum-free interval (PFI) (i.e., the period between the completion of first-line platinum-based chemotherapy and the initiation of second platinum therapy) and other clinicopathological features on the survival and the response to chemotherapy in women with advanced or recurrent cervical cancer.

Patients and methods

To be included in this analysis, patients had to satisfy all of the following conditions: (1) a histologic documented diagnosis of advanced or recurrent uterine cervical cancer; (2) prior treatment with two or more courses of initial chemotherapy with a platinum-based regimen including CCRT; (3) Second-line treatment with a platinum-based regimen with a PFI of at least 3 weeks and with the confirmation of tumor progression after receiving initial chemotherapy; (4) the response to second platinum therapy could be assessed on the basis of radiologic findings; and (5) no evidence of other cancers.

We retrospectively reviewed the medical charts of 65 patients who met all of the above criteria between 1996 and 2008 at National Cancer Center Hospital in Tokyo. Stage of disease was evaluated according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. The distribution of disease was evaluated by computed tomography or magnetic resonance imaging. We abstracted data on Eastern Cooperative Oncology Group (ECOG) performance status (PS), histology, the dates and contents of surgery, radiotherapy and chemotherapy.

The response to treatment was categorized by the best response achieved by the end of therapy and was determined by radiographic measurement of tumor. A complete response (CR) was defined as the disappearance of all disease for at least 4 weeks. A partial response (PR) was defined as a greater than 50% reduction in the product of perpendicular diameters obtained from the measurement of each lesion, sustained for at least 4 weeks. Progressive disease (PD) was defined as a greater than 50% increase in the product of perpendicular diameters of any lesion documented or the appearance of any new lesion. Stable disease (SD) was any condition not meeting any of the above three criteria. Survival was measured from the date of initiation of second platinum therapy to any cause of death or last contact. For the survival analysis, data on surviving patients without disease recurrence or progression were censored on the date of their last follow-up examination.

Statistical analyses were performed using Dr. SPSS II (SPSS Inc., Chicago, IL). We analyzed the predictors of response to second platinum therapy with the use of a logistic regression model and prognostic factors of survival with a Cox regression model. Univariate analyses were performed for each variable. Subsequently, the variables with a univariate result of $P < 0.07$ were included in the multivariate models. Models were selected by stepwise forward method, retaining variables significant at the $\alpha = 0.05$ level for our final model.

Results

Table 1 shows the clinical characteristics of the 65 patients. The median survival from the start of second platinum

Table 1 Patient characteristics

	No. of patients
Median age (years)	54 (28–73)
Performance status	
0	47
1	17
2	1
Histology	
Squamous cell carcinoma	47
Adenocarcinoma	10
Stage at initial diagnosis	
I	12
II	16
III	29
IV	8
Disease distribution before 2nd chemotherapy	
Pelvic	15
Extrapelvic	27
Both	23
Initial therapy	
CCRT	32
Surgery	21
Radiation	7
Chemotherapy	5
First-line chemotherapy	
CCRT (CCRT after surgery)	36 (4)
Chemotherapy (after surgery/after radiation)	29 (17/7)
Second platinum regimen	
Carboplatin + Irinotecan	27
Carboplatin + Paclitaxel	26
Cisplatin + Paclitaxel	5
Carboplatin	4
Platinum-free interval (months) Median 11.1 (0.7–66.6)	
0–8	27
9–17	18
1 ≥ 18	20

Table 2 Univariate analysis for response of second platinum therapy

Factor	No.	Response		
		Response rate (%)	Odds ratio (95% CI)	*P* value
Age				
>50	41		0.42 (0.13–1.29)	0.13
≤50	24			
PS				
0	30		0.23 (0.08–0.66)	0.006
1, 2	35			
Stage				
I, II	27		0.56 (0.20–1.55)	0.26
III, IV	38			
Histology				
Squamous cell carcinoma	47		1.18 (0.39–3.53)	0.77
Other	18			
Tumor size				
≤30 mm	28		0.38 (0.13–1.08)	0.068
>30 mm	37			
Liver metastasis				
Present	10		0.41 (0.10–1.63)	0.21
None	55			
Lung metastasis				
Present	23		0.67 (0.24–1.88)	0.45
None	42			
Extrapelvic disease				
Present	50		0.27 (0.06–1.08)	0.068
None	15			
First platinum therapy				
Chemoradiation	36		1.65 (0.61–4.47)	0.32
Chemotherapy alone	29			
Second platinum protocol				
Carboplatin based	58		0.20 (0.023–4.29)	0.15
Cisplatin based	7			
Platinum-free interval				
Continuous variable		42	0.93 (0.89–0.98)	0.008
≥6 months	51	45	0.31 (0.08–1.23)	0.096
<6 months	14			
≥9 months	38	53	0.27 (0.09–0.84)	0.034
<9 months	27			
≥12 months	28	57	0.24 (0.08–0.72)	0.029
<12 months	37			
≥18 months	20	65	0.21 (0.06–0.70)	0.013
<18 months	45			
≥24 months	11	81	0.06 (0.007–0.56)	0.008
<24 months	54			

therapy was 11.0 months (range, 1.1–66.6 months). The most common sites of abdominal disease at the start of second platinum therapy were the pelvis (58%), lung (32%), paraaortic lymph nodes (26%) and liver (17%). Twenty-four of 29 patients with stage IIIb disease and 5 of 15 patients with stage IIb had CCRT as initial treatment.

As first-line platinum chemotherapy, more than half of the patients received CCRT including cisplatin (40 mg/m^2/

Table 3 Multivariate analyses of response

Predictive factors	Response		
	Odds ratio	95% CI	*P* value
PFI ≥12 months	0.20	0.06–0.70	0.012
PS of 0	0.16	0.05–0.55	0.004
Tumor diameter ≤30 mm	0.18	0.05–0.70	0.013

Variables tested for inclusion in logistic regression model were age ≥50 y.o, PFI ≥12 months, PS of 0, tumor diameter ≤30 mm and extrapelvic disease

week for up to 6 doses) or nedaplatin (10 mg daily during pelvic radiotherapy). Nedaplatin was used in a phase II trial setting. The median number of administered courses was 4 (2–6) for cisplatin and 24 (15–28) for nedaplatin. Of the 29 patients who received first-line chemotherapy without radiotherapy, 18 were given carboplatin-based regimens and 11 were given cisplatin-based regimens. Between first and second platinum containing chemotherapy, more than two-thirds of the patients received no treatments; however, 15 patients received palliative radiotherapy.

For second platinum therapy, nearly 90% of the patients received carboplatin-based regimens, and most of the responses were achieved by carboplatin plus paclitaxel or carboplatin plus irinotecan. Carboplatin plus irinotecan was used in a phase II trial setting in our hospital.

Response to second platinum therapy

An overall response rate was 42% (95% confidence interval; 30–54%); six (9%) patients achieved CR and 21 (32%) achieved PR of second platinum therapy. Twenty-three (35%) patients had stable disease, and 15 (23%) had progressive disease. The response rate in the 36 patients who had received CCRT was 36%. The frequency of response increased in parallel with the length of the interval between platinum-based treatments.

The results of univariate logistic regression analysis of factors related to the response to second platinum therapy are shown in Table 2. Variables tested in the multivariate analysis were age, PS, a PFI for ≥12 months, a maximum tumor diameter ≤30 mm and extrapelvic disease. After controlling for these factors, a PFI for ≥12 months (OR, 0.20 [0.06–0.70]; $P = 0.012$), PS of 0 (OR, 0.16 [0.05–0.55]; $P = 0.004$) and a maximum tumor diameter ≤30 mm (OR, 0.18 [0.05–0.70]; $P = 0.013$) retained significance as independent predictors of response (Table 3).

Survival of second platinum therapy

The results of univariate analysis of survival, performed with a Cox regression model, are shown in Table 4. Survival curves according to a PFI for <6 months vs. ≥6 months are shown in Fig. 1. Variables tested in the multivariate analysis were age, PS, a PFI for ≥6 months and a histology of squamous cell carcinoma. A PFI for ≥6 months (hazard ratio [HR], 0.27 [0.13–0.55]; $P < 0.001$) and PS of 0 (HR 0.31 [0.17–0.55]; $P < 0.000$) retained significance as prognostic factors of survival.

Discussion

Present study indicated that the rate of response to second platinum therapy increased in parallel with the duration of the PFI and that the PFI has both predictive (PFI of 12 months) and prognostic (PFI of 6 months) value for second platinum therapy in women with advanced or recurrent cervical cancer. Our study failed to show that PFI of 6 months is predictive for response; however, this might be because of lack of sufficient sample size.

Increasing numbers of patients with uterine cervical cancer are receiving CCRT with cisplatin as primary treatment. Such patients are often given platinum-based regimens for second-line therapy. Response rates with cisplatin-based regimens are generally high but decrease in subgroups of patients who had received prior platinum-based chemotherapy, including CCRT [9, 10]. Therefore, the predictive and prognostic factors of second platinum therapy are needed to identify patients most likely to achieve favorable response and prognosis.

The overall response rate of 42% is higher than 22–29% reported by Monk [11]. This might be because of the smaller proportion (55%) of patients receiving prior primary CCRT compared with 70–81%. In our study, actually, the response rate showed higher as 52% in 29 patients without CCRT than that of 36% in 36 patients with CCRT.

Subgroup analyses of phase III trials comparing cisplatin alone with cisplatin plus topotecan showed that the probability of survival increased incrementally in both treatment groups, the longer a patient was from the completion of prior platinum-based therapy. The benefits of second platinum therapy were minimal in patients who relapsed within 6 months of prior platinum-based therapy and greatest in those in whom more than 2 years had elapsed from prior platinum-based therapy [12]. A phase II trial of oxaliplatin, a platinum derivative, in patients who previously received platinum-based combination chemotherapy reported a response rate of only 8.4%. However, the response rate was 22% in patients who had received prior platinum-based therapy more than 6 months before starting treatment with oxaliplatin, when compared with 0% in those who received prior platinum-based therapy within 6 months [13]. These results of prospective trials support those of our exploratory analyses.

Table 4 Univariate analysis on survival

Factor	No.	Survival	
		Hazard ratio (95% CI)	*P* value
Age			
>50	41	0.69 (0.40–1.19)	0.18
≤50	24		
PS			
0	30	0.23 (0.08–0.66)	<0.001
1, 2	35		
Stage			
I, II	27	1.13 (0.66–1.95)	0.74
III, IV	38		
Histology			
Squamous cell carcinoma	47	2.15 (1.11–4.14)	0.022
Other	18		
Tumor size			
≤30 mm	28	0.70 (0.40–1.19)	0.18
>30 mm	37		
Liver metastasis			
Present	10	0.69 (0.35–1.37)	0.29
None	55		
Lung metastasis			
Present	23	0.61 (0.35–1.08)	0.088
None	42		
Extrapelvic disease			
Present	50	0.69 (0.73–1.33)	0.29
None	15		
First platinum therapy			
Chemoradiation	36	1.36 (0.77–2.40)	0.30
Chemotherapy	29		
Second platinum protocol			
Carboplatin based	58	1.54 (0.55–4.29)	0.41
Cisplatin based	7		
Platinum-free interval			
≥6 months	51	0.22 (0.11–0.45)	>0.001
<6 months	14		
≥9 months	38	0.41 (0.23–0.72)	0.002
<9 months	27		
≥12 months	28	0.61 (0.35–1.07)	0.083
<12 months	37		
≥18 months	20	0.59 (0.33–1.08)	0.088
<18 months	45		
≥24 months	11	0.40 (0.17–0.95)	0.038
<24 months	54		

The results of our retrospective analyses and previous studiesl[21,22] suggest that the malignant cells in a subset of women with recurrent cervical cancer remain platinum-sensitive. Patients with a PFI of 24 months or longer had a greater than 80% chance of responding to platinum-based regimen. Second-line treatment with either a cisplatin- or carboplatin-based regimen thus appears to be one of the most promising therapeutic strategies for patients with a prolonged PFI in this clinical setting.

Our study had limitations. First, it was a retrospective study and lacked sufficient information on toxicity; we therefore cannot make firm recommendations for or against

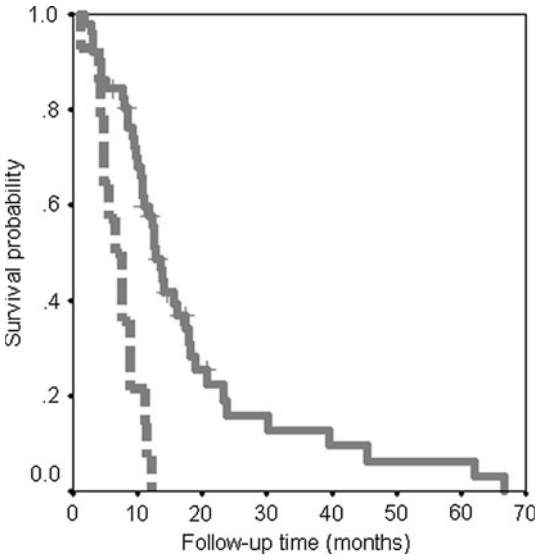

Fig. 1 Overall survival according to PFI. Survival curve according to a PFI for <6 months (*dotted line*) versus ≥6 months (*straight line*)

second platinum therapy. Second, nearly 90% of the patients received carboplatin-based regimens, which have not been proven to be superior to cisplatin-based regimen. Third, although this study was retrospective and exploratory analysis, the analyses of platinum-free interval were performed in multiple times. Despite the limitations of our study, the following general conclusions can be made. In patients with recurrent or metastatic cervical cancer who have received first-line platinum-based therapy, PFI and performance status might have both predictive and prognostic value for second platinum therapy. Response rates are expected to increase in parallel with the length of the PFI.

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55:74–108
2. Berek JS, Neville Hacker F (2005) Practical gynecologic oncology. Lippincott Williams & Wilkins, New York
3. Thigpen T, Shingleton H, Homesley H, Lagasse L, Blessing J (1981) Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a phase II study of the gynecologic oncology group. Cancer 48:899–903
4. Weiss GR, Green S, Hannigan EV, Boutselis JG, Surwit EA, Wallace DL, Alberts DS (1990) 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
5. Arseneau J, Blessing JA, Stehman FB, McGehee R (1986) 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
6. McGuire WP, Blessing JA, Moore D, Lentz SS, Photopulos G (1996) Paclitaxel has moderate activity in squamous cervix cancer. A gynecologic oncology group study. J Clin Oncol 14:792–795
7. Verschraegen CF, Levy T, Kudelka AP, Llerena E, Ende K, Freedman RS, Edwards CL, Hord M, Steger M, Kaplan AL, Kieback D, Fishman A, Kavanagh JJ (1997) Phase II study of irinotecan in prior chemotherapy-treated squamous cell carcinoma of the cervix. J Clin Oncol 15:625–631
8. Sutton GP, Blessing JA, Adcock L, Webster KD, DeEulis T (1989) Phase II study of ifosfamide and mesna in patients with previously-treated carcinoma of the cervix. A gynecologic oncology group study. Invest New Drugs 7:341–343
9. Long HJ III, Bundy BN, Grendys EC Jr, Benda JA, McMeekin DS, Sorosky J, Miller DS, Eaton LA, Fiorica JV (2005) 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
10. Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, Miller DS, Olt G, King S, Boggess JF, Rocereto TF (2004) 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
11. Monk BJ, Sill MW, McMeekin DS, Cohn DE, Ramondetta LM, Boardman CH, Benda J, Cella D (2009) 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
12. Long HJ III (2007) Management of metastatic cervical cancer: review of the literature. J Clin Oncol 25:2966–2974
13. Fracasso PM, Blessing JA, Wolf J, Rocereto TF, Berek JS, Waggoner S (2003) Phase II evaluation of oxaliplatin in previously treated squamous cell carcinoma of the cervix: a gynecologic oncology group study. Gynecol Oncol 90:177–180