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Phase II trial of paclitaxel and nedaplatin in patients with advanced/recurrent uterine cervical cancer: A Kansai Clinical Oncology Group study

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ABSTRACT

Objective. A multicenter phase II trial was conducted to evaluate the activity and toxicity of paclitaxel and nedaplatin (cis-diammineglycolatoplatonum) in patients with advanced/recurrent uterine cervical cancer.

Methods. Patients were required to have measurable disease. Histologic confirmation of the primary diagnosis as uterine cervical cancer was mandatory. The treatment consisted of paclitaxel 175 mg/m^2 over 3 hours and nedaplatin 80 mg/m^2 intravenously over 1 hour on day 1 every 28 days until progressive disease or adverse effects prohibited further therapy.

Results. Fifty patients were enrolled into the study protocol from October 2007 to February 2010. 45 patients(90%) were eligible for assessment of response (RECIST version 1.0) to treatment; 31 patients (62%) received prior radiotherapy and 23 patients (46%) received prior chemotherapy. The overall response rate was 44.4% (11 complete responses and 8 partial responses) with 22.2% of patients having stable disease. Grades 3 or 4 adverse events (NCI-CTCAE ver 3) included neutropenia ($n=16$, 32.7%), febrile neutropenia ($n=1$, 2.0%), anemia ($n=9$, 18.4%), but there was no significant thrombocytopenia. Non-hematologic toxicity was generally not serious and without a dominant pattern. The median progression-free survival was 7.5 months (95% C.I., 5.7, 9.4) and overall survival was 15.7 months (95% C.I., 9.4, 21.9).

Conclusions. Paclitaxel 175 mg/m^2 and nedaplatin 80 mg/m^2 intravenously on day 1 every 28 days in patients with advanced/recurrence uterine cervical cancer demonstrated easy administration, favorable antitumor activity, and the toxicity profile of this regimen would be decreased compared with cisplatin-containing combinations. Evaluation of this regimen in phase III trials is warranted.

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Introduction

Parkin et al. reported that 493,243 women were affected by uterine cervical cancer worldwide in 2002 [1], and in the United States advanced, recurrent, or persistent uterine cervical cancer accounted for an estimated 4210 deaths in 2010 [2]. Furthermore, this disease is a major health issue in certain areas of the world such as Central and South America.

For patients with recurrent or persistent disease, or distant metastasis, systemic chemotherapy is an important treatment option. The cytotoxic agents with demonstrable activity against squamous cell carcinoma of the uterine cervix include cisplatin (23–30%), ifosfamide (16%), paclitaxel (17%), and topotecan (12.5%) [3–6]. Unfortunately, the benefit of these agents has been only limited.

While cisplatin has been considered the corner stone of therapy for these patients, over 50 other agents have also been studied. The recent cooperative studies of the Gynecologic Oncology Group (GOG) and the Hellenic Cooperative Oncology Group (HeCOG) have demonstrated increased response rates, and in some cases improved survival, for combination regimens [7–9].

In 2009, Monk et al. conducted the randomized phase III trial (GOG protocol 204) of four cisplatin-containing doublet combinations, that

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was designed to evaluate the optimal cisplatin doublet among women with advanced or recurrent cervical cancer, and they reported that the trend in response rate, progression free survival, and overall survival favored paclitaxel and cisplatin (PC) arm compared with the other arms, although no significant statistical differences were detected [10]. This study represented a significant step forward in defining optimal therapy in this setting, however, the low response rate (29.1%) and relatively short overall survival (12.87 months) were disappointing. New agents that could improve front line or primary treatment are of particular interest.

Nedaplatin (cis-diammine glycolato platinum) is a cisplatin analogue which was developed as a less nephrotoxic agent in 1995 in Japan. Kato et al. reported that the response rate was 46.3% for cervical cancer [11], and the major side effect was hematotoxicity, while nephrotoxicity and neurotoxicity were rarely observed.

On the basis of the activity of paclitaxel and nedaplatin as single agents in the treatment of cervical cancer, the investigation of chemotherapy using these two agents for advanced, and recurrent cervical cancer is justified. Although the phase I study of the combination of paclitaxel and nedaplatin for uterine cervical cancer has not been reported, Yoshiike et al. reported the recommended dose of paclitaxel and nedaplatin were 180 mg/m^2 and 80 mg/m^2, respectively which resulted from a phase I study for non-small cell lung cancer [12]. Sekine et al. conducted a phase I study for un-resectable squamous cell carcinoma of lung and thymus, head and neck, and reported the recommended dose were 180 mg/m^2 of paclitaxel and 100 mg/m^2 of nedaplatin [13]. We considered that the results were reliable although the patients in these studies have not had prior pelvic radiation, so we initiated a phase II trial to evaluate the activity and toxicity of the combination of these two agents in 2007.

Materials and methods

Patients were treated according to Protocol G-0705 of the Kansai Clinical Oncology Group (KCOG). The KCOG Protocol Review Committee and each institutional Review Board approved this protocol. Written informed consent was obtained from all patients prior to enrollment.

Eligibility

Entry into the study required that patients have histologically confirmed stage IVB, recurrent, or persistent carcinoma of the cervix not amenable to curative treatment with surgery and/or radiation therapy. Histologic types included squamous cell carcinoma (SCC), adenosquamous cell carcinoma (ASCC), and adenocarcinoma (AC). Patients were allowed only one prior systemic chemotherapy regimen including platinum and/or taxane agents, and prior chemoradiation was counted as a systemic regimen. Patients were required to have measurable disease in two dimensions by CT scan or MRI. The other criteria included age, ranging from 20 to 70 and an ECOG performance status score 0–2. Patients were also required to have adequate hematologic (absolute neurrophil count; ANC$>=$1500/μl, platelets$>=$100,000/μl, hemoglobin$>=$10 g/dl), renal (creatinine$<=$1.5 mg/dl) and hepatic function (bilirubin$<=$1.5 mg/dl, sGOT/GPT$<=$100 U/L).

Patients were excluded from study participation if they had bilatelal hydronephrosis not amenable to decompression by either urethral stent or percutaneous drainage.

Treatment

Chemotherapy administration was as follows: paclitaxel 175 mg/m^2 over 3 hours plus nedaplatin 80 mg/m^2 over 1 hour on day 1 without much hydration every 28 days. Patients were premedicated with dexamethasone (20 mg) and ranitidine (50 mg) or famotidine (20 mg) intravenously 30–90 minutes prior to infusion. Diphenhydramine (50 mg) orally was also given 30 minutes prior to treatment. Chemotherapy was discontinued in cases of progressive disease or unacceptable toxicity, or patient's refusal.

All patients were required to have an ANC of more than 1.500/μl and a platelet count more than 100,000/μl on the day of re-treatment. Patients were removed from the study if their blood count had not recovered by 3 weeks after post-treatment date. Dose reduction levels for treatment modification of paclitaxel/nedaplatin were 150/70 mg/m^2 (level-1), 135/60 mg/m^2 (level-2), and 110/50 mg/m^2 (level-3). Patients requiring dose reductions to less than level-3 were removed from study.

Response and toxicity evaluation

The tumor response was defined according to the criteria adopted by the guideline of Response Evaluation Criteria in Solid Tumors (RECIST version 1.0) [14]. Target lesions included all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total. Complete response (CR) was defined as the complete disappearance of all target and nontarget lesions, with no development of new disease. Partial response (PR) was defined as a reduction by$>=$30% in the sum of the longest diameter of target lesions. Progressive disease (PD) was defined as an increase$>=$20% in the sum of the longest diameter of all target lesions or the appearance on one or more new lesions and/or unequivocal progression of existing nontarget lesions. Stable disease (SD) was defined as neither sufficient lesion shrinkage to quality for PR nor sufficient increase to quality for PD. Radiological studies were repeated every two cycles. If a patient was documented as having a CR or PR, the response was confirmed at least after 4 weeks from the first evidence of response. The overall survival (OS) was defined as the time from the date of registration until death or the date of last contact. The progression free survival (PFS) was defined as the time from the date of registration until the date of last contact, disease progression, or death, whichever came first.

Toxic effects were evaluated with respect to incidence and severity using the National Cancer Institute Common Toxicity Criteria, version 3.0 [15].

Statistical design

The primary endpoint of the current study was to assess the overall response rate, and the secondary endpoints were to assess the feasibility, PFS, and OS. An analysis of historical phase II trials [3–6,8,9,11] indicate that the response rate was expected to be 40% or more, and 20% or less was not of interest. The study was designed with 80% power such that the lower limit of the 95% confidence interval (CI) for the estimate of the response rate was >0.05. A sample size of 43 assessable patients was required. The Kaplan–Meier method was used to estimate overall and progression free survival.

Results

Fifty patients were entered into this trial from 9 institutions between October 2007 and February 2010. One patient never received the study drugs because of her death before the protocol treatment. Four were not evaluable for response having had insufficient assessment of tumor response. Thus, 49 patients (98%) were assessed toxicity, and 45 patients (90%) were eligible for assessment of response rate.

The baseline characteristics of patients are listed in Table 1. The mean patient age was 54.3 years with a range of 26–89 years. Histological types included thirty-two cases SCC (64%), 12 ASCC (24%), and 1 ACC (2%). Thirty-one patients (62%) received prior radiotherapy and 23 patients (46%) received prior chemotherapy. A median of

Table 1
Patient characteristics ($n=50$).

Characteristics	Number
Age, mean years (range)	54.3 (26–89)
Performance status, *n* (%)	
0	31 (62)
1	9 (18)
2	4 (8)
Unknown	6 (12)
Pathology, *n* (%)	
SCC	32 (64)
Non-SCC	13 (26)
Unknown	5 (10)
Stage, *n* (%)	
IVB	9 (18)
Recurrence	35 (70)
Unknown	6 (12)
Prior chemotherapy, n(%)	23 (46)
Prior platinum regimen	23 (46)
Prior taxane regimen	3 (6)
Prior radiotherapy, *n* (%)	31 (62)
Prior surgery, *n* (%)	15 (30)
Sites of disease, *n* (%)	
Intra-pelvis	28 (56)
Extra-pelvis	16 (32)
Unknown	6 (12)
Progression free interval, *n* (%)	
0–12 months	26 (52)
>12 months	9 (18)
Unknown	15 (30)

four cycles were administered to each patient with a range of 1–16 cycles.

The overall response rate was 44.4% (11 complete responses, 9 partial responses). Stable disease occurred in 10 (22.2%) patients. Therapeutic benefit (CR + PR + SD) was observed in 31 (66.6%) patients (Table 2). When the responses were stratified according to the pathological type, clinical responses were documented in 40.6% (13/32) of patients with SCC and 53.9% (7/13) of patients with non-SCC, although the difference was not statistically significant.

The other variables were assessed for their possible prognostic value for objective response, such as, stage (IVB or recurrence), mode of primary treatment (with or without chemotherapy / radiotherapy), sites of disease (intra-pelvis or extra-pelvis), and time from primary diagnosis to disease recurrence (within 12 months or more). Only sites of disease were a statistically significant predictor of response (Table 3).

Grades 3 and 4 adverse events are described in Table 4. Major toxicities were primarily hematologic, with 32.7% of patients experiencing grades 3 and 4 neutroperia, and 18.4% of patients experiencing grades 3 and 4 anemia, but there was no significant thrombocytopenia. One patient had grade 3 febrile neutropenia, which resolved itself easily without granulocyte-colony stimulating factor. Two patients had treatment delay because of myelosupression. Non-hematologic toxicity was generally not serious and without a dominant pattern. In particular, dose limiting neuropathy was uncommon (only 1 patient with grade 3 neuropathy). No patients had dose reduction, but 3 patients were withdrawn from the protocol because of allergic reaction (nedaplatin related).

Table 2
Objective response ($n=45$).

Tumor response					
	CR	PR	SD	PD	NE[a]
N (%)	12 (26.7)		8 (17.8)	10 (22.2)	13 (28.9)
2	(4.4)				

[a] not evaluable.

Table 3
Best overall response, by strata. pathology; SCC vs non-SCC, stage; recurrence vs IVb, prior chemotherapy; yes vs no, prior radiotherapy; yes vs no, sites of disease; intra-pelvis vs extra-pelvis, progression free interval; 0–12 months vs more than 12 months.

	Tumor response, *n* (%)			
	N	CR/PR	Others	*p*-Value
Pathology				
SCC	32	13 (40.6)	19 (59.4)	0.419
non-SCC	13	7 (53.8)	6 (46.2)	
Stage				
IVB	9	4 (44.4)	5 (55.6)	0.967
recurrence	35	15 (42.9)	20 (57.1)	
Prior chemotherapy				
yes	23	10 (43.5)	13 (56.5)	0.967
no	21	9 (42.9)	12 (57.1)	
Prior radiotherapy				
yes	31	12 (38.7)	19 (61.3)	0.355
no	13	7 (53.8)	6 (46.2)	
Sites of disease				
intra-pelvis	28	7 (25.0)	21 (75.0)	0.001
extra-pelvis	16	12 (75.0)	4 (25.0)	
Progression free interval				
0-12 months	26	9 (34.6)	17 (65.4)	0.094
>12 months	9	6 (66.7)	3 (33.3)	

The median progression free survival for all patients was 7.5 months (95% C.I., 5.7, 9.4) (Fig. 1). The median overall survival for all patients was 15.7 months (95% C.I., 9.4, 21.9) (Fig. 2).

Discussion

For a number of years, cisplatin has been the most active drug for the treatment of cervical cancer [3], with the response rate of about 20% to 30%. Striving to improve on these limited results, many studies have been conducted in an attempt to identify other active agents to be used alone or in combination with cisplatin.

The phase III GOG study reported by Moore et al. (GOG 169) showed that adding paclitaxel to cisplatin increased the objective response rate from 19% to 36%($p=0.002$). The median PFS was also increased from 2.8 months to 4.8 months ($p<0.001$), but there was little difference in median OS (8.8 month vs 9.7 months) [7].

The next phase III GOG study in the same setting was reported by Long et al. (GOG 179), in which cisplatin plus topotecan was compared with cisplatin [8]. This was the first randomized, prospective phase III trial to demonstrate a statistically significant survival advantage for combination chemotherapy. The combination arm had a superior outcome in improving survival from 6.5 months to 9.4 months ($p=0.017$).

There was a difference between GOG 169 and GOG 179. The GOG 169 study was completed during the transition to concurrent

Table 4
Grades 3 and 4 toxicities ($n=49$).

Toxicities	*N* (%)	
	Grade 3	Grade 4
Hematological toxicities		
Neutropenia	13 (26.5)	3 (6.1)
Febrile neutropenia	1 (2.0)	0
Anemia	2 (4.1)	7 (14.3)
Thrombocytopenia	0	0
Non-hematological toxicities		
Elevated serum Cre level	3 (6.1)	0
Allergy	0	1 (2.0)
Anorexia	1 (2.0)	0
Constipation	1 (2.0)	0
Fatigue	1 (2.0)	0
Myalgia/arthrargia	2 (4.1)	0
Sensory neuropathy	1 (2.0)	0
Infection	2 (4.1)	0

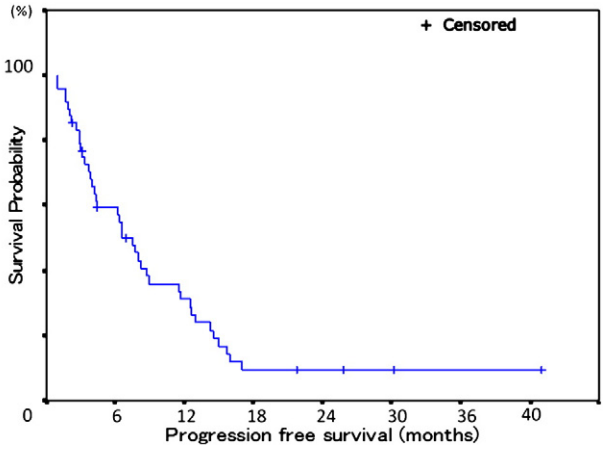

Fig. 1. Kaplan–Meier curve for progression-free survival. Median PFS (months) = 7.5 (95%CI = 5.7, 9.4).

chemoradiotherapy (CCRT) for the locally advanced cervical cancer, while the GOG 179 study was conducted after the transition. The question whether the result of GOG 179 defined the optimal regimen for advanced or recurrent cervical cancer remained unanswered given the new era of CCRT. The lack of survival advantage in GOG 169 may be a result of the lack of prior radio sensitizing chemotherapy.

In GOG 204 trial, which was designed to evaluate the optimal cisplatin doublet among women with advanced or recurrent cervical cancer, the investigators indicated that the PC arm should represent the control arm for future randomized phase III trials [10].

This current study was designed to evaluate the activity and toxicity of the combination of pactitaxel plus nedaplatin and our overall response rate of 44.4% is comparable to that seen in previous reports of combination regimen, nevertheless the current study included 63.3% of patients who received prior radiotherapy. In phase II trials with PC therapy, Rose et al. showed the response rate was 46.3%, and Papadimitriou et al. showed 47% [16,17], however, in those studies, only 37% or 35% patients received prior radiotherapy. In GOG 204 which included 70% patients who received radiotherapy, the overall response rate of the same regimen was only 29% [10].

Although it has been considered that non-SCC of uterine cervix was resistant to the chemotherapy [18], Curtin et al. reported that in their phase II study with paclitaxel, the response rate of this population was 31% [19]. In the current study, the overall response of non-SCC was 53.8% (7/13), which is a much better response than we expected.

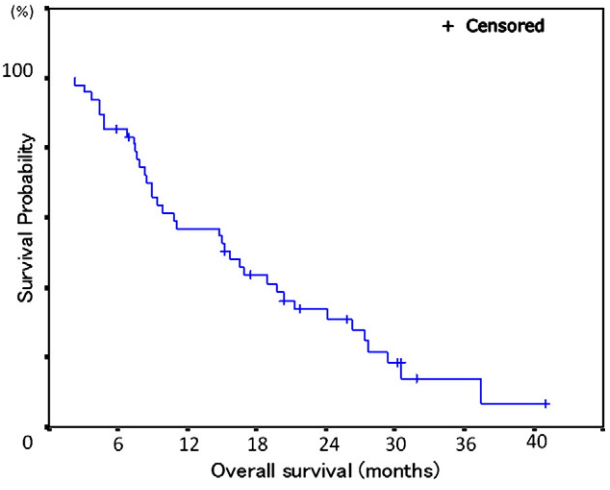

Fig. 2. Kaplan–Meier curve for overall survival. Median OS (months) = 15.7 (95%CI = 9.4, 21.9).

The primary toxicity of this paclitaxel and nedaplatin combination was neutropenia, with neutropenic fever occurring in 2.0%, which was anticipated based on previous reports. In PC arm of GOG 204, severe neutropenia also occurred in 78.2% [10].

It was surprising that no patients experienced grade 3 or 4 thrombocytopenia, which led to the speculation that the platelet-sparing effect would occur on this combination, just as that was reported when paclitaxel was combined with carboplatin [20].

Neurotoxicity is the one of the main toxicities for cisplatin and paclitaxel. Papadimitriou et al. reported that in their phase II study with PC therapy, 53% of their patients developed some degree of neurotoxicity, including grade 3 neurotoxicity in 9% [16]. Connelly et al. reported that in their experience of PC to patients with gynecologic cancer, there was a 71% incidence of neurotoxicity, 20% of which was grade 3 or 4 [21]. In this study, grade 3 or 4 neurotoxicity occurred in only 1 patient (2.0%).

Some patients among this population will have, or already have had, ureteral obstruction leading to renal dysfunction, restricting or precluding the use of cisplatin.

Nedaplatin, which was developed as a less nephrotoxic agent, could be administered more safely and easily than cisplatin, but there were three patients who had grade 3 renal dysfunction in the current study. This is why hydronephrosis happened in two patients and massive bleeding from the cervix happened in one patient due to the disease progress during the protocol study. We considered that there is no relation between this therapy and severe renal dysfunction.

In summary, our combination of paclitaxel and nedaplatin was administered easily, relatively well tolerated, and has a favorable response rate compared with cisplatin-containing combinations previously studied [3,4,7–10,16,17]. Further evaluation of the combination of paclitaxel and nedaplatin combination is warranted in future phase III trials.

Conflict of interest statement

This paper has not been published elsewhere and all authors have contributed substantially to its contents. Furthermore, there are no financial relationships, and/or conflict of interest between the authors and the subject of this manuscript.

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