Feasibility Study of Docetaxel and Nedaplatin for Recurrent Squamous Cell Carcinoma of the Uterine Cervix

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Abstract. *Background: To determine a new taxane plus platinum treatment regimen for squamous cell carcinoma of the uterine cervix (CSCC), a phase I feasibility study of docetaxel (DTX) plus nedaplatin (CDGP) combination therapy was conducted. Patients and Methods: Twenty consecutive patients were enrolled into the study. The starting dose of DTX/CDGP was 60 mg/m^2 / 80 mg/m^2, every 4 weeks for at least three courses and the dose was escalated to 70 mg/m^2 / 100 mg/m^2. DTX 60 mg/m^2 / CDGP 100 mg/m^2 was also evaluated as an extra dose level. Results: Dose-limiting toxicity was granulocytopenia and the maximum tolerated dose was determined as 70 mg/m^2 / 100 mg/m^2. All 20 patients had measurable disease and a partial response was achieved in 8 (40.0%) patients. Conclusion: DTX/CDGP therapy appears to be a tolerable regimen for cervical squamous cell carcinoma, even in patients previously treated by cisplatin concurrent chemoradiotherapy. The recommended doses of DTX and CDGP were determined to be 60 mg/m^2 and 100 mg/m^2, respectively.*

Previous phase III studies of chemotherapy for recurrent or advanced squamous cell carcinoma of the uterine cervix (CSCC) (1-4) have revealed that cisplatin is the key chemotherapeutic drug; the addition of bleomycin did not improve patient survival and combined treatment with paclitaxel or topotecan plus cisplatin yielded superior survival to that with cisplatin alone. Combined paclitaxel and cisplatin (TP) therapy is thought to be an effective regimen, because the Gynecologic Oncology Group (GOG) 169 trial (3) reported an overall response rate of 46% even among patients with recurrent CSCC with a history of having undergone radiation therapy. However, TP therapy includes several problems such as the inconvenience of 24 hour administration of paclitaxel and the high incidence of neurotoxicity. Since *in vitro* (5) and *in vivo* (6) studies have reported the efficacy of *cis*-diammine (glycolato) platinum (CDGP; Nedaplatin), especially in cases of squamous cell carcinoma, the effects of CDGP-based combination chemotherapy have been studied in carcinoma of the uterine cervix (7), esophagus (8) and head and neck (9). Moreover, a recent phase I/II study of irinotecan plus CDGP therapy reported an overall response rate of 68% , including 2 complete responses in 27 patients with advanced or recurrent CSCC (7). Docetaxel (DTX) had a significantly lower neurotoxicity than and comparable activity with paclitaxel combined with carboplatin for ovarian cancer (10). In patients with advanced or recurrent CSCC, single agent docetaxel demonstrated tumor activity with a response rate of 13% (11). Therefore, to determine the feasibility of DTX/CDGP as an optional regimen for patients with CSCC, a phase I study was conducted in patients with recurrent CSCC.

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Patients and Methods

The present study was conducted as a phase I dose escalation study. The protocol was approved by the Institutional Review Committee of Kinki University School of Medicine, and full informed consent was obtained from all the patients prior to their enrollment in the study. The eligibility criteria for inclusion in the study are shown in Table I. The criteria for starting the next treatment course are shown in Table II. DTX/CDGP treatment was planned for 4-weekly administration, beginning at an initial dose of DTX 60 mg/m^2 and CDGP 80 mg/m^2, with the dose escalated to 70 mg/m^2 / 80 mg/m^2, 70 mg/m^2 / 90 mg/m^2 and 70 mg/m^2 / 100 mg/m^2. However, since the highest dose level was considered to be the maximum tolerated dose (MTD) and at the second highest dose level disease progression was observed (see Results), an additional dose level (60 mg/m^2 / 100 mg/m^2) was evaluated. CDGP (Aqupla; Shionogi & Co. Ltd, Osaka, Japan) was administered intravenously over 90 minutes, followed by intravenous administration of DTX (Taxotere; Sanofi-Aventis K.K., Tokyo, Japan) over 90 minutes. Premedication prior to the administration of DTX consisted of the intravenous administration of dexamethasone (8 mg)

Table I. *Eligibility criteria*.

1.	Recurrent uterine cervical squamous cell carcinoma
2.	Measurable region to determine direct effects of chemotherapy
3.	Performance status ≤ ECOG 2
4.	Normal ECG
5.	No active infectious diseases or active inflammatory diseases
6.	Leukocyte count ≥4,000/mm^3 and <12,000/mm^3
7.	Granulocyte count ≥2,000/mm^3
8.	Platelet count ≥100,000/mm^3
9.	Hemoglobin level ≥9.0 g/dl
10.	Serum total bilirubin ≤1.5 mg / dl
11.	Normal serum creatinine
12.	GOT, GPT within 2 x normal value
13.	Full informed consent from patient obtained

ECOG: Eastern Cooperative Oncology Group; ECG: electrocardiogram; GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyrubic transaminase.

Table II. *Criteria for starting next treatment course*.

1.	Leukocyte count ≥3,000/mm^3 and <12,000/mm^3
2.	Granulocyte count ≥1,500/mm^3
3.	Hemoglobin level ≥8.0 g/dl
4.	Platelet count ≥50,000/mm^3
5.	Performance status ≤ECOG 2
6.	Normal ECG
7.	GOT, GPT within 2.5 x normal value
8.	Serum creatinine within normal limit
9.	Fever <38.0˚C
10.	Non-hematological toxicity* CTCAE ≤ Grade 1
11.	No progressive disease

ECOG: Eastern Cooperative Oncology Group; ECG: electrocardiogram; GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyrubic transaminase; CTCAE: Common Terminology Criteria for Adverse Events, 2003. *Not including nausea, vomiting, and alopecia.

and granisetron (3 mg) over 30 minutes and hydration with a total intravenous fluid volume of 2000 ml. Granulocyte-colony stimulating factor (G-CSF) support was only employed for those patients who exhibited Common Terminology Criteria for Adverse Events (CTCAE) grade 4 neutropenia or febrile neutropenia and none of the patients received prophylactic G-CSF supplementation. The dose-limiting toxicities (DLTs) were defined as grade 4 granulocytopenia lasting for over 5 days, grade 4 thrombocytopenia, febrile neutropenia (granulocytopenia ≤,1000/mm^3 and body temperature ≥38.5˚C, grade 3/4 non-hematological toxicity excluding nausea, vomiting, and alopecia or treatment delay of more than 6 weeks due to toxicity. Toxicity was graded by the National Cancer Institute Common Toxicity Criteria, version 2.0. Three patients were entered at the initial dose level and monitored for DLT. If no DLT was observed, three additional patients were treated at the next higher dose level until DLT was observed or the maximum dose level was reached in the absence of DLT. If one of the three patients developed DLT at any level, the cohort was expanded to three additional patients, and if no DLT was observed in the three additional cases, the treatment dose was escalated to the next level. Maximum tolerated dose (MTD) was determined as the dose level at which no more than one out of six patients experienced a DLT. The direct antitumor effects were determined based on the criteria proposed in the new guidelines to evaluate the response to treatment in solid tumors (12).

Table III. *Characteristics of patients*.

Number of patients	20
Mean age (range)	52.4±8.0 years (28-66)
PS	
0	8
1	10
2	2
Prior treatment	
CCRT alone	7
RT alone	2
RH alone	2
RH + adjuvant CCRT	6
RH + adjuvant RT	3
Recurrent site	
Prior irradiation area	9
Extra irradiation area	7
Both	2
No prior irradiation	2
Median no. of treatment courses (range)	5.5 (1-11)

PS: Performance status determined by Eastern Cooperative Oncology Group Criteria; CCRT: cisplatin concurrent chemoradiotherapy; RT: radiation; RH: radical hysterectomy.

Results

Between August 2004 and November 2006, a total of 20 patients were enrolled into the study. The clinicopathological characteristics of the patients are listed in Table III. Table IV shows results of the present phase I dose escalation study. Among the patients receiving the DTX/CDGP therapy, 1 out of the 6 patients developed DLT (neutropenia) at level 3 (DTX 70 mg/m^2 / CDGP 90 mg/m^2), and 2 out of the 5 patients developed DLT (neutropenia with a delay of planned treatment by over 2 weeks and febrile neutropenia) at level 4 (DTX 70 mg/m^2 / CDGP 100 mg/m^2). Six out of the 17 patients (35.3%) given dose levels 1-4 showed a partial response. At dose levels 1 and 3, disease progression was observed. Three patients given the extra dose level (DTX 60 mg/m^2 / CDGP 100 mg/m^2) had no DLT. Two out of the 3 patients at this dose level showed a partial response. Disease progression was not observed at this dose level. Two patients had received no radiation therapy, four patients had disease within the irradiation field and two patients had disease outside the irradiation field among the patients who responded to DTX/CDGP.

Leukopenia (75.0%) and granulocytopenia (85.0%) were the most frequently observed CTCAE grade 3/4 hematological toxicities, and 12 patients (60.0%) needed G-CSF support. Other grade 3 toxicities observed were

Table IV. *Summary for each dose level.*

Dose level	DTX CDGP	Number of patients	Prior therapy	Total treatment courses	DLT	Best response
1	60 mg/m^2	3	CCRT	6		SD
	80 mg/m^2		CCRT	3		PD
			RT	7		SD
2	70 mg/m^2	3	RH+RT	6		SD
	80 mg/m^2		RH+RT	6		PR
			CCRT	6		SD
3	70 mg/m^2	6	CCRT	11		SD
	90 mg/m^2		CCRT	3		PR
			RH+CCRT	2	NEU	PD
			RH	8		PR
			RH	6		PR
			RH+CCRT	4		PD
4	70 mg/m^2	5	RH+RT	5		PR
	100 mg/m^2		CCRT	2	FN	SD
			RH+CCRT	4		SD
			RH+CCRT	3		PR
			CCRT	1	NEU	SD
EX	60 mg/m^2	3	RH+CCRT	7		PR
	100 mg/m^2		RT	11		PR
			RH+CCRT	3		SD

DTX: Docetaxel; CDGP: nedaplatin; CCRT: cisplatin concurrent chemoradiation; RT: radiation therapy; RH: radical hysterectomy; DLT: dose limiting toxicity; NEU: neutropenia; FN: febrile neutropenia; SD: stable disease; PR: partial response; PD: progressive disease; EX: extra dose level.

anemia (2 patients), thrombocytopenia (1 patient), nausea (5 patients), and vomiting (1 patient). Two patients exhibited a grade 1 allergic reaction soon after the start of DTX administration. None of the patients exhibited neurotoxicity. All of the patients with adverse effects, including those with DLTs, recovered within 3 weeks and no treatment-related deaths were observed.

Discussion

Dose level 4 (DTX 70 mg/m^2 / CDGP 100 mg/m^2) was determined as the MTD for DTX/CDGP, and three patients at level 1 and 3 had disease progression. In contrast, the three patients at the extra dose level (DTX 60 mg/m^2 / CDGP 100 mg/m^2) had no DLT and two of these patients responded to the DTX/CDGP. Therefore the recommended treatment dose for a subsequent phase II study was determined as the extra dose level, DTX 60 mg/m^2 / CDGP 100 mg/m^2, administered every 4 weeks. While the effects of platinum-based combination chemotherapy alone for recurrent CSCC have been unsatisfactory, survival benefit of CCRT both as a primary therapy (13-16) and an adjuvant therapy (17) has been shown in patients with CSCC. CCRT has been widely used as the standard treatment for patients with CSCC. However, the treatment options for recurrent CSCC after CCRT are limited because the overall response rate to platinum-based chemotherapy in cases of recurrent CSCC has been reported to be around 20% (18) in chemotherapy-naive patients, and 5.3% (19) in patients with recurrent disease within the previously irradiated field. Therefore, the establishment of an effective chemotherapeutic regimen for CCRT-treated patients with recurrent CSCC is urgently needed to improve the long-term prognosis of such patients. Based on the results of our present study, CDGP-based chemotherapy may be effective even for cases with disease within the previous irradiation field, although the treatment results remain unsatisfactory.

The efficacy (9-13% for overall response) of DTX alone was limited for patients with advanced or recurrent CSCC who had received previous chemotherapy (11, 20). Subsequent studies should be planned carefully to observe the efficacy of DTX/CGDP. Large-scale phase II studies of DTX/CDGP and the combination of CDGP and paclitaxel as another taxane for a calibration may be needed to discover a therapy improving the long-term prognosis of patients with recurrent CSCC previously treated by CCRT or radiation therapy.

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