Weekly Cisplatin, Infusional High-dose 5-Fluorouracil and Leucovorin for Advanced, Recurrent and Metastatic Cervical Carcinoma

SHENG-MOU HSIAO[1,2], CHI-AN CHEN[2], CHIUN HSU[3], HO-HSIUNG LIN[2], CHANG-YAO HSIEH[2] and LIN-HUNG WEI[2,3]

[1]Department of Obstetrics and Gynecology, Far Eastern Memorial Hospital, Pan-Chiao, Taipei, Taiwan; Departments of [2]Obstetrics and Gynecology, and [3]Oncology, National Taiwan University College of Medicine and National Taiwan University Hospital, Taipei, Taiwan, R.O.C.

Abstract. *Background: To evaluate the effectiveness and toxicity of infusional cisplatin and weekly 24-hour infusion of high-dose fluorouracil plus leucovorin (P-HDFL) for the treatment of patients with stage IVB, recurrent and metastatic carcinoma of the cervix. Patients and Methods: A phase II study of P-HDFL in stage IVB, recurrent and metastatic carcinoma of cervix was initiated in January 2001. As of March 2007, a total of 21 patients were enrolled. Of these, 16 were evaluable for response. Results: The overall objective response rate was 25% [95% confidence interval (CI), 1.2-48.8%] with none achieving complete response. The median progression-free survival and overall survival for all 21 patients was 2.3 months (95% CI, 1.2-4.3 months) and 10.5 months (95% CI, 4.6-17.4 months), respectively. Toxicity was tolerable. The main problems were nausea/vomiting and anemia. Conclusion: P-HDFL appears to be a moderately effective regimen with low toxicity for treating patients with advanced, recurrent and metastatic cervical cancer.*

Carcinoma of the uterine cervix is the second leading malignancy affecting women worldwide. Although the frequency of advanced cervical cancer has been reduced through early diagnosis by the use of PAP-smear screening and improved treatment of locoregionally advanced disease by multimodality therapy, recurrent and metastatic disease remains a major cause of cancer death in women (1).

Chemotherapy is appropriate for patients with recurrent, metastatic, or persistent carcinoma of the cervix for whom treatment with potentially curative intent is no longer amenable. In these patients, the role of chemotherapy has been directed at improved survival and palliation of symptoms while trying to maintain an acceptable level of toxicity.

The most active single chemotherapeutic agents for carcinoma of the cervix include cisplatin, paclitaxel, topotecan, vinorelbine, and ifosfamide (1). Single-agent cisplatin is considered the standard chemotherapeutic agent in the treatment of advanced, recurrent and metastatic cervical cancer, with response rates in the range of 15-30% (1-3). Bonomi *et al.* reported that increasing the dose of cisplatin (from 50 to 100 mg/m^2) increased the objective response rate but not the progression-free survival or overall survival (4). However, toxicities increased substantially when the dose intensity increased more than 50 mg/m^2 every 3 weeks. Because of the emetogenicity and nephrotoxicity of high doses, it is not advisable to administer such doses to certain patients with advanced carcinoma of the cervix (4). An effort to develop a combination therapy with improved efficacy and minimal or no increase in toxicity is therefore warranted.

Single-agent 5-fluorouracil (5-FU) has modest activity (4.2%-9.6%) against carcinoma of the cervix (5). The biochemical modulation of 5-FU with sufficient leucovorin increases thymidylate synthase inhibition by stabilizing the ternary complex between 5-FU and thymidylate synthase (6). Cisplatin and 5-FU have been reported to act synergistically (7, 8) and be effective in the treatment of metastatic and recurrent cervical cancer (9, 10). Previous reports have shown that a weekly 24-hour infusion of high-dose fluorouracil (2, 600 mg/m^2) plus leucovorin (300 mg/m^2) (known as the HDFL regimen) with an infusion route is active against various types of cancer at surprisingly low bone marrow toxicities (11, 12). As the HDFL regimen has repeatedly been demonstrated to cause minimal myelosuppression (11-13), it is an ideal component for combination chemotherapy with

Correspondence to: Dr. Lin-Hung Wei, MD, Ph.D., Department of Oncology, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, 100, Taiwan, R.O.C. Tel: +886223123456 ext 7140, Fax: +886223711174, e-mail: weilh1966@gmail.com

Key Words: Cisplatin, 5-fluorouracil, recurrent cervical cancer, metastasis.

Table I. *Clinicopathological features of the 21 patients receiving P-HDFL.*

Characteristic	No. of patients	%
Performance status (ECOG score)		
0	1	5
1	8	38
2	12	57
Pathology		
Squamous cell carcinoma	18	86
Adenocarcinoma	3	14
FIGO stage at diagnosis		
IB	7	33
IIA	4	19
IIB	3	14
III	2	10
IV	5	24
Previous therapy		
Surgery	1	5
Surgery, radiation	4	19
Radiation, chemotherapy	9	43
Surgery, chemotherapy	2	10
Surgery, radiation, chemotherapy	1	5
Chemotherapy	2	10

Table II. *Site of lesion in relation to previously irradiated area in the 21 patients receiving P-HDFL.*

		Relation to previously irradiated area		
Lesion	Total (n=21)	Outside (n=12)	Inside (n=4)	Outside + inside (n=5)
Single lesion				
Pelvis	3	0	3	0
Lung	1	1	0	0
Distant	0	0	0	0
Multiple lesions				
Pelvis + lung	0	0	0	0
Pelvis + distant	7	1	1	5
Distant + lung	6	6	0	0
Distant	1	1	0	0
Pelvic + lung + distant	3	3	0	0

other cytotoxic agents against carcinoma of the cervix. This phase II study was conducted to evaluate the effectiveness and toxicity of infusional cisplatin and weekly 24-hour infusion of high-dose fluorouracil plus leucovorin (P-HDFL) for the treatment of advanced, recurrent and metastatic carcinoma of the cervix.

Patients and Methods

From January 2001 to March 2007, a total of 21 patients with stage IVB, metastatic or recurrent cervical cancer were enrolled in the study. Recurrences were confirmed by histopathological examinations. Patients were required to have a normal serum creatinine level (≤1.3 mg/dL) or a measured creatinine clearance of ≥40 mL/min (12, 14), total bilirubin ≤2 mg/dL, and transaminase ≤3x the upper normal limit. In addition, patients needed to have disease measurable by radiographic studies (plain X-ray, computed tomography or magnetic resonance imaging scans), no serious active underlying medical issues, and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. All patients provided written informed consent before undergoing treatment. Ethical approval for this study was obtained from the Research Ethics Committee of the National Taiwan University Hospital.

The P-HDFL regimen was given as follows: In each 28-day cycle, patients received two separate 24-h infusions of cisplatin at 45 mg/m^2 on days 1 and 8, and 5-FU 2, 600 mg/m^2 plus leucovorin 300 mg/m^2 intravenous 24-h infusion on days 1, 8 and 15. Normal saline hydration (≥1,000 mL), dexamethasone and antiemetics (ondansetron or granisetron) were given prophylactically before each dose of cisplatin. Criteria for undergoing the day 8 and 15 doses were white blood cell count ≥2000 cells/μL, platelet count ≥50,000 per μL and serum creatinine ≤1.5 mg/dL.

Physical examination, survey of adverse reactions and hemogram check-up of patients were performed before administering each dose of the P-HDFL treatment. Tumor response and toxicity were evaluated according to the World Health Organization criteria (15). A complete response (CR) was defined as the disappearance of all measurable disease for at least 4 weeks. A partial response (PR) was defined as a 50% or more reduction in the products of each measurable lesion for at least 4 weeks. Progressive disease (PD) was defined as a 25% or more increase in the size of one or more measurable lesions, or the appearance of new lesions. Stable disease (SD) was defined as any condition not meeting any of the above criteria.

Progression-free survival was measured from the date of first chemotherapy dose to the date of documented disease progression, death due to other causes, or last follow-up. Overall survival was measured from the date of first chemotherapy to date of death, or last follow-up. Progression-free and overall survival were estimated using the Kaplan-Meier method (16). Univariate analysis of survival was performed by the log-rank test (17).

Results

From January 2001 to March 2007, a total of 21 patients with stage IVB, recurrent or metastatic cervical cancer had been treated with this regimen at the National Taiwan University Hospital. The clinicopathological characteristics of these patients are tabulated in Table I. The median age was 54 years (range: 36-82 years). Among sixteen patients with recurrent or metastatic cervical cancer, six had undergone prior chemoradiotherapy as initial curative therapy, and three had received prior salvage chemotherapy for recurrent or metastatic lesions, including 1 course of cisplatin/ifosfamide regimen and 4 courses of cisplatin/ paclitaxel regimen (n=1), 3 courses of paclitaxel/ifosfamide/ cisplatin regimen (n=1), and 4 courses of cisplatin chemotherapy (n=1). Furthermore, two of four patients with stage IVB cervical cancer had received prior chemotherapy with 3 to 4 courses of

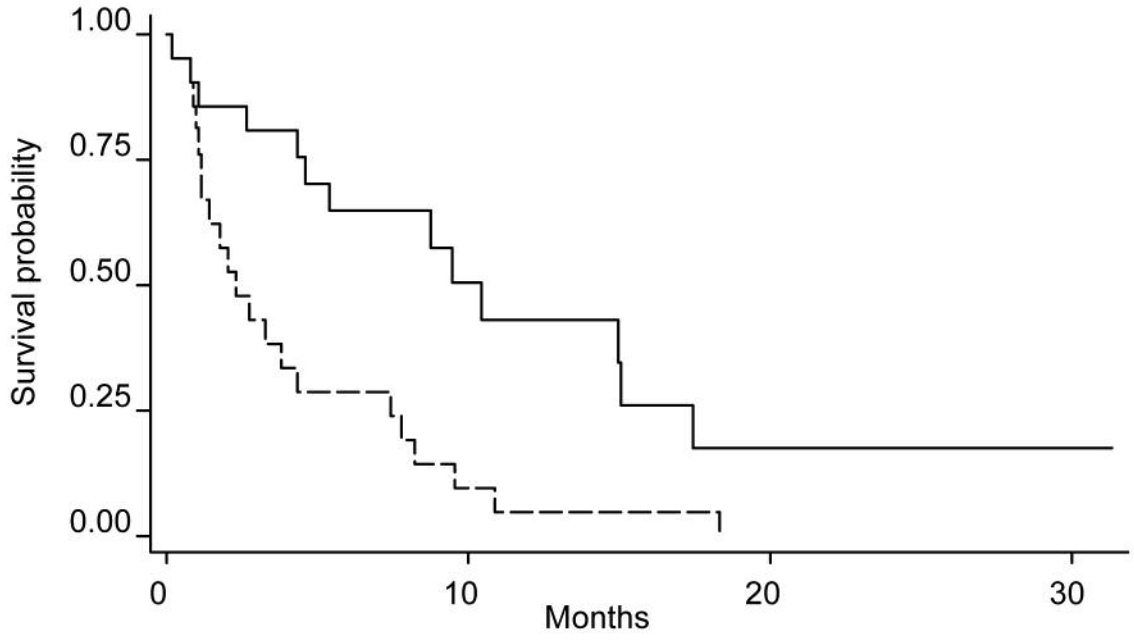

Figure 1. *Progression-free (dashed line) and overall (solid line) survival curves.*

methetrexate/ vinblastine/ doxorubicin/cisplatin regimen. Sites of tumor lesions in relation to previous irradiated areas are shown in Table II.

A total of 65 courses of P-HDFL were administrated. The mean cycle number given was 3.1 cycles per patient (range, 1-8 cycles). Schedule modification was necessary in two patients as a result of grade 3 leukopenia.

Among the 16 patients eligible for response evaluation, none achieved CR while 4 (25 %) achieved PR, with an overall objective response rate of 25% [95% confidence interval (CI), 1.2%-48.8%]. Of the 21 patients, 5 dropped out and were not eligible for response evaluation. Among these five patients, three dropped out because of rapid deterioration of performance status; one because of rapid progression of disease status, and subsequently receiving bleomycin and ifosfamide treatment; and one patient, without experiencing significant toxicity, refused further treatment after the first cycle of P-HDFL treatment and received supportive care only. Of the 21 patients, 8 had SD and 4 had PD. The median progression-free and overall survival for all 21 patients was 2.3 months (95% CI, 1.2-4.3 months) and 10.5 months (95% CI, 4.6-17.4 months), respectively (Figure 1). Responses related to previous irradiated areas are tabulated in Table III. The response rate (3/9; 30%) for patients with lesions outside previously irradiated areas (PIA) was higher than those with lesions inside PIA (0%), and those with lesions both outside and inside PIA (25%); however, there were no differences in survival (p=0.33, log-rank test) between these groups.

All of the 21 patients were eligible for evaluation of toxicity. The toxicity profile is summarized in Table IV. There were no cisplatin allergies. The most common grade 3 or 4 toxicity was anemia (n=4). Grade 3 leukopenia occurred in only one patient. There were no grade 3 or 4 thrombocytopenias. Grade 3 nausea/vomiting occurred in two patients, while grade 3 stomatitis occurred in one. Two patients had grade 2 nephrotoxicity; in both patients, right ureteral obstructions due to tumors were noted after one or two courses of P-HDFL treatment. The blood urea nitrogen and creatinine values markedly improved after right nephrostomy.

Discussion

Single-agent cisplatin has long been the treatment of choice for managing patients with recurrent or metastatic cervical cancer. A series of phase II and III clinical trials has recently demonstrated that an active single agent, including ifosfamide, paclitaxel and topotecan, combined with cisplatin improved the objective response rate and progression-free survival (18-20). Nevertheless, an overall survival advantage has only been demonstrated for topotecan plus cisplatin (20). In this study, the response rate (25%) and median progression-free survival (2.3 months) associated with the P-HDFL regimen were not superior to those associated with commonly used regimens, such as cisplatin alone (response rate 20% and progression-free survival 3-5 months) (1), cisplatin plus ifosfamide

Table III. *Responses related to previous irradiated area, median progression-free survival and median overall survival on months in the 21 patients receiving P-HDFL.*

	Relation to previous irradiated area				Survival (months)	
Clinical response	Outside (n)	Inside (n)	Outside + inside (n)	Total (n)	Progression-free	Overall
Complete response	0	0	0	0	-	-
Partial response	3	0	1	4	3.2	-
Stable disease	4	3	1	8	7.4	31.3
Progressive disease	2	0	2	4	1.0	13.5
Not evaluable	3	1	1	5	0.8	-

(response rate 31% and progression-free survival 4.6 months), cisplatin plus paclitaxel (response rate 36% and progression-free survival 4.8 months), and cisplatin plus topotecan (response rate 27% and progression-free survival 4.6 months) (18-20); however, the median overall survival (10.5 months) was superior or comparable to those of commonly used regimens, such as cisplatin alone (6 months), cisplatin plus paclitaxel (9.7 months) and cisplatin plus topotecan (9.4 months) (1, 19, 20).

P-HDFL was originally designed to be a low-toxicity regimen and has proven to be so (7, 13, 21). Although the dose of 5-FU in HDFL is much higher than that of the conventional bolus 5-FU regimens, the likelihood of developing grade 3 or 4 hematological toxicities has been reported to be below 3% (11). The mechanisms of low marrow toxicities by the continuous infusion of HDFL have been attributed to the putative ''blood–marrow barrier'' which allows only 15% to 20% 5-FU to penetrate into the bone marrow at low blood concentrations (less than 15 μM) of 5-FU (13). In this study, the most common adverse events of the P-HDFL regimen were hematological; however, grade 3 or 4 leukopenia was low (5%), compared with a cisplatin plus topotecan regimen (63.3%), cisplatin plus paclitaxel (52.7%), and cisplatin plus gemcitabine (31.3%) (19, 20, 22).

The favorable toxicity and comparable efficacy of the P-HDFL regimen make it a viable option for patients with recurrent or metastatic carcinoma of the cervix who have been heavily treated with radiotherapy and/or chemotherapy. However, there is clearly a need for more effective chemotherapy regimens in this patient population. The characteristics of P-HDFL might make it an ideal backbone for introducing a third active agent, such as paclitaxel, docetaxel and methotrexate, into the regimen for fit patients (23-25). For example, a recent study showed that paclitaxel combined with P-HDFL improved efficacy in patients with metastatic urothelial carcinoma without increased toxicity (23).

Carcinoma of the cervix is one of the biggest killers of women in developing countries. Women with lower socioeconomic status appear to have a higher risk of cervical cancer (26). Accordingly, the cost of health care is an issue for these patients, particularly when deciding whether to use a drug with a higher acquisition cost. The P-HDFL regimen is markedly less expensive than cisplatin/paclitaxel, cisplatin/topotecan and cisplatin/gemcitabine regimens. In Taiwan, for a female patient with a body surface of 1.5 m^2, the drug cost of P-HDFL ($111 per cycle) is much cheaper than that of cisplatin (50 mg/m^2) plus paclitaxel (135 mg/m^2) ($633 per cycle), cisplatin (50 mg/m^2) plus topotecan (0.75 mg/m^2 days 1 to 3) ($386 per cycle), and cisplatin (30 mg/m^2 day 1 and 8) plus gemcitabine (800 mg/m^2 day1 and 8) ($598 per cycle) (19, 20, 22). Furthermore, at the time of writing, the National Health Insurance in Taiwan did not cover the cost of topotecan, paclitaxel and gemcitabine for treatment of recurrent and metastatic cervical cancer. Though the continuous infusion used in P-HDFL might be inconvenient to ambulatory patients, this inconvenience can be circumvented by a portable device containing a small bag connected to a minipump that controls the infusion rate (12).

Table IV. *Toxicity profile of the 21 patients receiving P-HDFL.*

	No. of patients (%) with WHO toxicity grades			
	1	2	3	4
Hematological				
Leukopenia	2 (10)	5 (24)	1 (5)	0
Thrombocytopenia	1 (5)	1	0	0
Anemia	3 (14)	7 (33)	4 (19)	0
Infection	0	2 (10)	0	0
Non-hematological				
Nausea	4 (19)	3 (14)	2 (10)	0
Vomiting	2 (10)	1 (5)	2 (10)	0
Diarrhea	0	1 (5)	0	0
Stomatitis	0	1 (5)	1 (5)	0
Nephrotoxicity	0	2 (10)	0	0
Hepatotoxicity	0	0	0	0
Neurotoxicity	2 (10)	1 (5)	0	0
Hand-and-foot syndrome	0	1 (5)	0	0

In conclusion, considering its cost effectiveness and low toxicity, the P-HDFL regimen for stage IVB, recurrent and metastatic cervical cancer appears to be a viable option. A randomized trial comparing P-HDFL with alternative regimens of palliative chemotherapy is warranted to confirm its therapeutic role in treating patients with cervical cancer.

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Received January 23, 2008
Revised March 26, 2008
Accepted March 27, 2008