Comparison of concurrent chemoradiotherapy with cisplatin plus 5-fluorouracil versus cisplatin plus paclitaxel in patients with locally advanced cervical carcinoma

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Objective: The aim of this study was to compare survival outcomes and toxicities between concurrent radiotherapy with cisplatin plus 5-fluorouracil and that with cisplatin plus paclitaxel in patients with locally advanced cervical carcinoma.

Methods: We retrospectively reviewed data from 93 locally advanced cervical carcinoma patients (stage IB to IVA) who had been treated by concurrent radiotherapy with cisplatin plus 5-fluorouracil (CF, n=45) vs. cisplatin plus paclitaxel (CP, n=48) as primary therapy. Toxicities and survival outcomes were compared.

Results: In the CP group, there were higher frequencies of severe (grade 3 or 4) leukopenia (79.2%, as compared to 11.1% in the CF group), severe neutropenia (77.1%, as compared to 8.9% in the CF group) and severe peripheral neuropathy (12.5%, as compared to 2.2% in the CF group). In the CF group, there were higher frequencies of severe nausea (33.3%, as compared to 14.6% in the CP group) and severe hyponatremia (11.1%, as compared to 0% in the CP group). Five-year DFS of the CF and CP groups was 67.4% and 79.1%, respectively (p=NS). Five year OS of the CF and CP groups was 79.6% and 80.9%, respectively (p=NS).

Conclusion: Concurrent radiotherapy with cisplatin plus paclitaxel showed increased leukopenia, neutropenia and peripheral neuropathy, but less gastrointestinal toxicity (nausea) than that with cisplatin plus 5-fluorouracil. Survival outcome between these two groups was not statistically different in this study. Large prospective randomized controlled studies will be needed to confirm this result.

Key Words: Cervical cancer, Chemoradiotherapy, Cisplatin, 5-fluorouracil, Paclitaxel

INTRODUCTION

Since the National Cancer Institute (NCI) released a clinical announcement regarding concurrent chemoradiation in 1999,¹ chemoradiotherapy with cisplatin-containing agents became a new standard therapy for locally advanced cervical cancer. The five randomized trials which lead to the NCI clinical announcement used four different cisplatin-containing regimens with radiotherapy.²⁻⁶ In the five trials, different doses, cycles, and combinations of cisplatin based chemotherapy used. All these cisplatin based regimens with radiation showed survival benefit over radiation alone. Based on

these randomized trials, it is evident that cisplatin-containing chemoradiation has a survival benefit over radiation alone. However, several questions regarding chemoradiation remain unanswered by these randomized trials. One of these questions is what will be the best ideal chemoradiation regimen.

The roles of chemotherapy during chemoradiation are to eradicate micrometastases and sensitize tumor cells to radiation.⁴ For this purpose, chemotherapeutic agents should have anti-cancer activity against cervical cancer cells and behave as a radiosensitizer. The rationales of using paclitaxel in combination with cisplatin in concurrent chemoradiation are that 1) paclitaxel acts as a radiosensitizer *in vitro*,^{7,8} 2) a phase I study with cisplatin plus paclitaxel has proved excellent overall response in patients with locally advanced cervical cancer,⁹ and 3) cisplatin plus paclitaxel have activity against metastatic and recurrent cervical cancer.¹⁰

Recently, several studies which used cisplatin plus paclitaxel with concurrent radiation have been reported.^{9,11-13} These were phase I and/or II studies which focused on evaluating toxicities and response rates in a limited number of enrolled patients. These studies have demonstrated that cisplatin plus

Received December 27, 2008, Revised February 7, 2009,
Accepted February 13, 2009

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paclitaxel concurrently used with radiation show encouraging response rate and good tolerability. In the studies, dose limiting side effects were hematologic toxicities and diarrhea. However, to the best of our knowledge, there have been no head-to-head comparison studies in concurrent chemoradiotherapy between cisplatin plus paclitaxel and cisplatin plus 5-fluorouracil (5-FU). Therefore, this study aims at comparing survival outcomes and toxicities between cisplatin plus 5-FU and cisplatin plus paclitaxel used in concurrent chemoradiotherapy in patients with locally advanced cervical carcinoma.

MATERIALS AND METHODS

1. Patients

One hundred sixty five patients with histologically proven cervical carcinoma underwent primary concurrent chemoradiation at the Daegu Catholic Medical Center in Daegu, Korea between 2000 and 2007. Among the patients, the medical records of one hundred fifty nine patients were available for evaluation. One hundred twelve patients were treated with cisplatin plus 5-fluorouracil ($n=52$) or cisplatin plus paclitaxel ($n=60$). The other 47 patients underwent chemoradiation with weekly cisplatin regimen, and most patients (40) were diagnosed and treated after 2005.

This retrospective study included patients with the following criteria: 1) histologically proven cervical carcinoma, 2) Stage IB to IVA disease, 3) concurrent chemoradiation with cisplatin plus 5-fluorouracil or cisplatin plus paclitaxel, 4) for the purpose of cure, 5) squamous cell carcinoma, adenocarcinoma or adenosquamous histology, 6) no para-aortic lymph node metastasis in the magnetic resonance imaging (MRI) findings, and 7) no previous treatment history. The stage of disease was determined clinically according to the FIGO staging system. Stage IB and IIA patients in this study were those with lymph node metastasis by MRI, bulky tumor (over 4 cm in diameter), or suspected deep stromal invasion, who were anticipated to require postoperative chemoradiation. With these inclusion criteria, 93 patients (45 in cisplatin plus 5-fluorouracil group [CF group], 48 in cisplatin plus paclitaxel group [CP group]) were included in this study.

2. Treatment

All patients received pelvic with/without extended field radiation and concurrent cisplatin based chemotherapy. The pelvis was treated by external beam radiotherapy with a linear accelerator using photon beam energy of 6/15 MV within a standard four-field box technique, followed by high dose rate brachytherapy. The energy of 6 MV was used selectively only in anteroposterior and posteroanterior teletherapy for the patients whose pelvic anteroposterior diameters were less than 20 cm before 2005, but these patients were treated with 15 MV in both lateral teletherapy. Patients with Stage IB and IIA cervical carcinoma received a dose of 4,500-5,040 centigrays

(cGy) as external beam in 25-28 fractions over 5.0-5.5 weeks. Patients with Stage IIB to IVA cervical carcinoma received a dose of 5,040-5,400 cGy as external beam radiotherapy given in 28-30 fractions over 6 weeks. This was followed by six courses of high dose intracavitary brachytherapy, after external beam radiotherapy was completed. A dose of 3,000 cGy in 6 fractions was given over 3 weeks.

Two cycles of chemotherapy during external beam radiotherapy were given and consisted of cisplatin (75 mg/m^2) with 5-FU ($4,000 \text{ mg/m}^2$), or cisplatin (75 mg/m^2) with paclitaxel (135 mg/m^2). There were no specific criteria choosing cisplatin plus 5-FU or paclitaxel, except the patient's personal economic reasons because of the higher cost of paclitaxel. Chemotherapy started at the commencement of radiotherapy (day 1) and was given at 3 week intervals. Chemotherapy with cisplatin and 5-fluorouracil consisted of an intravenous infusion of 75 mg/m^2 of cisplatin (day 1), followed by an intravenous infusion of $4,000 \text{ mg/m}^2$ of 5-fluorouracil over a 96-hour period (days 2-5). One liter of normal saline was given both before and after cisplatin, and mannitol was used to increase urine output (day 1). Premedication included ondansetron and dexamethasone to reduce nausea and vomiting. Chemotherapy with cisplatin plus paclitaxel consisted of an intravenous infusion of 135 mg/m^2 of paclitaxel (day 1), followed by an intravenous infusion of 75 mg/m^2 of cisplatin (day 2). After concurrent chemoradiation, an additional two cycles of chemotherapy (3rd cycle: day 63-70, 4th cycle: day 84-91) were given as adjuvant chemotherapy in some patients. There were no specific criteria for adjuvant chemotherapy, but we had used adjuvant chemotherapy before 2005. If patients had grade 3 or 4 leukopenia or neutropenia, granulocyte macrophage colony stimulating factor (GM-CSF) was used. Dose reduction was indicated when patients had severe hematologic or non-hematologic toxicities. Chemotherapy was stopped when severe toxicities were persistent after dose reduction, when patients had poor performance status, or when patients refused it.

3. Evaluation of toxicities and follow up

Patients were evaluated at the beginning of treatment and then weekly for side effects. A complete blood count and a biochemistry profile were also performed. Complete blood cell counts were obtained at days 10 to 14 of each chemotherapy cycle for evaluation of nadir white blood cell (WBC), neutrophil, hemoglobin (Hb), and platelet. At days 10 to 14 of each chemotherapy cycle, we obtained a questionnaire from patients regarding nausea, vomiting, diarrhea, tingling sensation, fatigue, general condition and etc. The lowest nadir complete blood counts (CBC) level and the worst toxicity of each category of non-hematologic toxicity during treatment were used for analysis of toxicity. The toxicity of chemoradiation was determined according to the 'common terminology criteria for adverse events v3.0 by NCI'.

To evaluate the clinical response, we checked physical ex-

amination, Pap smear and imaging studies after 3 months from the end of radiation. After treatment, we followed up patients at 3 month intervals for the first 2 years, and then at 4-6 month intervals for additional 3 years, and once a year thereafter.

4. Determination of lymph node metastasis

As we did not apply surgical staging in patients with cervical cancer, lymph node metastasis was evaluated by MRI. The criteria of lymph node metastasis by MRI were lymph nodes that were over 1 cm in the short axis diameter and were enhanced with gadolinium in T1 weighted enhanced magnetic resonance imaging.

5. Study end point

Primary end point was the comparison of survival outcome according to chemotherapy regimens. Overall survival (OS) was defined as the time from the date of diagnosis to death from cervical cancer. Patients who survived beyond the time of analysis were censored at the time of their last follow-up date. Disease free survival (DFS) was defined as the time from date of diagnosis to the recurrence of cancer in any sites. The evaluations of hematologic and non-hematologic toxicities were the secondary end points of this study.

6. Statistical analysis

Comparisons of variables between the groups were based on the chi-square test and t-test. The OS and DFS were estimated by the life-table method of Kaplan-Meier. Differences in survival rates were assessed by the log-rank test. p-values were the result of two-sided tests and p-value < 0.05 was considered statistically significant. Statistical analysis was done using SPSS ver. 13 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Characteristics of patients

Ninety three patients met with the previously described inclusion criteria. Forty five patients were treated with cisplatin plus 5-FU (CF group), and 48 patients were treated with cisplatin plus paclitaxel (CP group). The mean ages for patients of the CF and CP groups were 49.9 ± 8.2 years (mean $\pm$ standard deviation) and 50.9 ± 10.7 years, respectively. FIGO stage distributions of the two groups were not statistically different, and pathologic types, tumor diameters determined by MRI, and pretreatment squamous cell carcinoma (SCC) antigen levels were also not different as shown in the Table 1. Because we did not perform surgical staging of the cervical cancer, we checked possible lymph node metastasis by MRI, as described above. The frequencies of pelvic lymph node metastasis of both groups were not statistically different. The frequencies of parametrial invasion determined by physical examination were not statistically different. The pretreatment levels of WBC, neutrophil, Hb, and platelet were similar in

both groups (Table 1). All patients were Gynecologic Oncology Group performance status of 0 or 1 before beginning of the treatment.

2. Chemotherapy

The majority of patients completed their scheduled chemotherapy during external beam radiotherapy, but three patients received only one cycle of chemotherapy due to either severe toxicities or poor performance status. Seventy one patients received one or two additional cycles of chemotherapy after radiotherapy (Table 2). The patients of both groups received similar total cycles of chemotherapy (CF vs. CP group: 3.3 ± 0.9 vs. 3.1 ± 0.9 cycles, $p = \text{NS}$). All patients received at least one cycle of chemotherapy. There were 10 patients in the CF group, and 27 patients in the CP group who required dose reduction during chemotherapy due to severe toxicities ($p = 0.001$). Eleven patients in the CF group and 12 patients in the CP group stopped their scheduled chemotherapy due to

Table 1. Characteristics of patients

Variables	CDDP+5FU (N=45)	CDDP+ Paclitaxel (N=48)	p-value
Age (yr, mean $\pm$ SD)	49.9 $\pm$ 8.2	50.9 $\pm$ 10.7	NS*
Stage			
IB1	6 (13.3%)	9 (18.7%)	NS [†]
IB2	3 (6.7%)	7 (14.6%)	
IIA	4 (8.9%)	6 (12.5%)	
IIB	22 (48.9%)	18 (37.5%)	
III	9 (20.0%)	6 (12.5%)	
IVA	1 (2.2%)	2 (4.2%)	
Pathologic type			
SCC	41 (91.1%)	38 (79.2%)	NS [†]
ADC or ASC	4 (8.9%)	10 (20.8%)	
Tumor diameter (cm, mean $\pm$ SD)	4.0 $\pm$ 1.3	4.4 $\pm$ 1.5	NS*
Initial SCC Ag. Level (ng/ml, mean $\pm$ SD)	6.7 $\pm$ 10.2	5.5 $\pm$ 7.3	NS*
Parametrial invasion	32 (71.1%)	28 (58.3%)	NS [†]
Pelvic LN metastasis	14 (31.1%)	15 (31.3%)	NS [†]
Past history			
Tuberculosis	1	3	NS [†]
Hypertension	3	3	
Diabetes	1	4	
Hepatitis	2	1	
Others	3	3	
Pretreatment CBC (mean $\pm$ SD)			
Leukocyte (count/mm ³)	7,356 $\pm$ 2,235	7,220 $\pm$ 2,856	NS*
Neutrophil (count/mm ³)	4,834 $\pm$ 2,326	4,597 $\pm$ 2,421	NS*
Hemoglobin (g/dl)	11.5 $\pm$ 1.3	11.9 $\pm$ 1.4	NS*
Platelet (count/mm ³)	261,267 $\pm$ 56,129	273,083 $\pm$ 73,149	NS*

CDDP: cisplatin, 5FU: 5-fluorouracil, SD: standard deviation, NS: no statistically significant difference, SCC: squamous cell carcinoma, ADC: adenocarcinoma, ASC: adenosquamous carcinoma, LN: lymph node, CBC: complete blood count

*independent samples t-test, [†]chi-square test

Table 2. The number of received cycles of chemotherapy

No. of cycles	CDDP+5FU (N=45)	CDDP+Paclitaxel (N=48)	p-value
1	1	2	NS*
2	8	11	
3	11	14	
4	25	21	
<i>Mean of received cycles of chemotherapy (mean±SD)</i>			NS [†]
3.3±0.9 3.1±0.9			

CDDP: cisplatin, 5FU: 5-fluorouracil, SD: standard deviation, NS: no statistically significant difference

*chi-square test, [†]independent samples t-test

Table 3. Worst hematologic toxicities during treatment

	CDDP+5FU (N=45)	CDDP+Paclitaxel (N=48)	p-value
<i>Hematologic toxicity evaluated by the worst nadir values (mean±SD)</i>			
WBC	2,971±1,065	1,619±925	<0.001*
ANC	1,971±900	717±823	<0.001*
Hb	9.5±1.1	9.5±0.9	NS*
Platelet	159,089±49,032	156,521±56,930	NS*
<i>Hematologic toxicity evaluated by grade of the worst nadir values (no.)</i>			
Leukopenia			
Grade 1	5	1	<0.001 [†]
Grade 2	22	7	
Grade 3	5	29	
Grade 4	0	9	
Neutropenia			
Grade 1	3	1	<0.001 [†]
Grade 2	10	6	
Grade 3	2	10	
Grade 4	2	27	
Anemia			
Grade 1	4	12	NS [†]
Grade 2	31	26	
Grade 3	3	3	
Grade 4	0	0	
Thrombocytopenia			
Grade 1	21	19	NS [†]
Grade 2	0	2	
Grade 3	0	1	
Grade 4	0	0	

Some of patients had more than adverse effect. Grades of toxicities were evaluated by 'Common terminology criteria for adverse events version 3.0 by National Cancer Institute'

CDDP: cisplatin, 5FU: 5-fluorouracil, SD: standard deviation, NS: no statistically significant difference

*independent samples t-test, [†]chi-square test

severe toxicities or poor performance status (p=NS). Two patients in the CF group and 3 patients in CP group refused chemotherapy during treatment.

3. Hematologic toxicities

Although both groups had similar values of pretreatment CBC, the means of nadir leukocyte (CF vs. CP group: 2,971±

Table 4. Worst non-hematologic toxicities during treatment

	CDDP+5FU (N=45)				CDDP+Paclitaxel (N=48)				p-value*
	G1	G2	G3	G4	G1	G2	G3	G4	
Gastrointestinal									
Nausea	7	15	15	0	10	22	7	0	0.033 [†]
Vomiting	13	13	3	0	15	8	0	0	NS
Diarrhea	13	4	10	0	9	14	9	0	NS
Hypersensitivity	0	1	0	0	0	10	2	0	0.006
Peripheral neuropathy	1	7	1	0	4	14	6	0	0.018
Alopecia	9	3	0	0	2	9	0	0	0.022
Hyponatremia	2	0	4	1	3	0	0	0	0.024 [†]
Hypokalemia	8	0	1	0	4	2	1	0	NS
Hepatotoxicity	6	1	1	0	11	4	2	0	NS
Renal toxicity	0	1	0	0	1	0	0	0	NS

Some of patients had more than one adverse effect. Grades of toxicities were evaluated by 'Common terminology criteria for adverse events version 3.0 by National Cancer Institute'

CDDP: cisplatin, 5FU: 5-fluorouracil, NS: no statistically significant difference

*chi-square test, [†]statistically significant difference over grade 3 toxicity, [‡]CDDP+5FU group showed more grade 3 or 4 hyponatremia

1,065 vs. 1,619±25) and neutrophil (1,971±900 vs. 717±823) counts were significantly lower in the CP group, as compared to the CF group. The frequency of grade 3 or 4 leukopenia in the CP group (79.2%) was significantly higher than the CF group (11.1%). The frequency of grade 3 or 4 neutropenia in the CP group (77.1%) was also significantly higher than the CF group (8.9%). The frequencies of anemia or thrombocytopenia were not statistically different between these two groups (Table 3).

4. Non-hematologic toxicities

With regard to gastrointestinal toxicity, grade 3 nausea was more common in the CF group (CF vs. CP group: 33.3% vs. 14.6%, p=0.033). The frequencies of vomiting, anorexia, diarrhea, gastritis, and colitis were similar between these groups. The frequencies of grade 2 alopecia, peripheral neuropathy, and hypersensitivity were higher in the CP group, as shown in Table 4. The frequency of hyponatremia (Grade 3 or 4) was higher in the CF group, but that of hypokalemia was similar in these groups. Hepatotoxicity or renal toxicity was not different (Table 4). There was one patient in the CF group who had premature ventricular contractions during chemotherapy, and there were two patients in the CP group who had radiation colitis after treatment.

5. Treatment outcome

Eighty six patients (92.5%) demonstrated complete clinical response to chemoradiation, whereas 7 patients (7.5%) demonstrated partial response to treatment. Response rates of both groups were not statistically different (complete re-

sponse rates in the CF and CP groups: 93.3% and 91.7%). Five patients showing partial response underwent adjuvant hysterectomy after chemoradiation (2 patients in the CF group and 3 patients in the CP group). After a median follow up of 47.3 (2.1-88.4) months, 24 patients developed recurrent disease, 16 patients died from their disease and one patient died of a cause other than cervical cancer (sepsis due to gastric ulcer perforation). Patterns of recurrence in both groups were not statistically different (local and pelvic recurrence rates of the CF and CP groups: 11.1% and 4.2%, systemic recurrence rates of the CF and CP groups: 24.4% and 16.7%). Two patients had both local and systemic recurrent lesions at the time of diagnosis of recurrence (Table 5). Five-year DFS of the CF and CP groups were 67.4% and 79.1%, respectively ($p=NS$), and 5 year OS of the CF and CP groups were 79.6% and 80.9%, respectively ($p=NS$) (Fig. 1).

Table 5. Clinical response and type of recurrence

	CDDP+5FU (N=45)	CDDP+Paclitaxel (N=48)	p-value*
Clinical response			
CR	42 (93.3%)	44 (91.7%)	
PR [†]	3 (6.7%)	4 (8.3%)	NS
Stable/progressive	0	0	
Recurrence [‡]			
Local	5 (11.1%)	2 (4.2%)	NS
Systemic [§]	11 (24.4%)	8 (16.7%)	NS

CDDP: cisplatin, 5FU: 5-fluorouracil, CR: complete response, PR: partial response, NS: no statistically significant difference

*chi-square test, [†]Two patients of CDDP+5FU group and three patients of CDDP+Paclitaxel group underwent adjuvant hysterectomy,

[‡]A total of 24 patients had recurrent disease, 2 of them had local and systemic recurrence together at the time of diagnosis of recurrence,

[§]Systemic recurrence included paraaortic lymph node metastasis and other systemic metastases

DISCUSSION

In this study, we observed that concurrent radiation with cisplatin plus paclitaxel resulted in more severe leukopenia and neutropenia, but less gastrointestinal toxicity than that with cisplatin plus 5-FU in patients with locally advanced cervical carcinoma. In particular, 77.1% patients of the cisplatin plus paclitaxel group experienced at least one event of grade 3 or 4 neutropenia during chemotherapy, which was the dose limiting side effect in this study. It is notable that the dosage of cisplatin and 5-FU was determined based upon the a previous randomized trial.⁴ The total number of chemotherapy cycles was also determined in accordance with a previous report.⁵ In general, the usual dosage of paclitaxel is 135-175 mg/m² every 3 weeks. Considering toxicity which might be caused by the combination therapy of cisplatin and radiation, a dosage of 135 mg/m² every 3 weeks was used in this study as the initial dose of paclitaxel. The frequencies of leukopenia and neutropenia of the cisplatin plus paclitaxel regimen were higher than previously reported.^{11,12} For example, in a phase I/II study of the Gynecologic Oncology Group using cisplatin (40 mg/m²/wk) and paclitaxel (40 mg/m²/wk) for 6 cycles, 17.7% and 11.5% of the total administered cycles show grade 3 or 4 leukopenia and grade 3 or 4 neutropenia, respectively.¹¹ In another phase II trial with cisplatin (75 mg/m²) plus paclitaxel (175 mg/m²) every 3 weeks for four cycles, 25% and 16% patients display grade 3 or 4 leukopenia and grade 3 or 4 neutropenia, respectively.¹² The reason why our study shows a higher frequency of leukopenia and neutropenia might be explained by a dosage effect, i.e., 4 cycles of paclitaxel (135 mg/m²) combined with cisplatin and radiation in this study might be too much for Asian women. This is in accordance with a Japanese study which reported that the grades of hematological toxicity are significantly greater in weekly cisplatin

Fig. 1. (A) Kaplan-Meier estimates of disease free survival among patients undergoing chemoradiotherapy with cisplatin plus 5-fluorouracil (n=45) or plus paclitaxel (n=48). (B) Kaplan-Meier estimates of overall survival among patients undergoing chemoradiotherapy with cisplatin plus 5-fluorouracil (n=45) or plus paclitaxel (n=48).

treatment groups at 40 mg/m² (conventional dose in chemoradiation) than at 30 mg/m².¹⁴ However, we observed no difference in the frequencies of anemia and thrombocytopenia between the cisplatin plus paclitaxel and cisplatin plus 5-FU regimens. This is also in agreement with previous reports.^{11,12}

With regard to gastrointestinal toxicity, patients with the cisplatin plus 5-FU regimen experienced nausea more commonly than those with the cisplatin plus paclitaxel regimen. However, both regimens showed a similar degree of vomiting and diarrhea. Generally, 5-FU is known to result in severe gastrointestinal toxicity than paclitaxel.¹⁵ In other non-hematologic toxicities, hypersensitivity, such as urticaria or itching was more common in patients with the cisplatin plus paclitaxel regimen, although it was mild to moderate, such as urticaria or itching. Both cisplatin and paclitaxel are known to cause peripheral neuropathy. Accordingly, neuropathy was more commonly observed in patients with the cisplatin plus paclitaxel regimen. In contrast, there was no severe renal toxicity in both regimens, probably due to the routine use of massive hydration and mannitol when cisplatin was administered. The cisplatin plus 5-FU regimen showed a higher frequency of grade 3 or 4 hyponatremia, as opposed to the cisplatin plus paclitaxel regimen. This might be due to longer IV infusion time per each cycle and/or poor oral intake resulting from nausea in patients with the cisplatin plus 5-FU regimen. However, grade 2 alopecia was more commonly observed in the cisplatin plus paclitaxel regimen, whereas grade 3 or 4 alopecia was not detected in both regimens. This might be explained by the fact that paclitaxel is a stronger inducer of alopecia than 5-FU.¹⁵

In this study, we did not observe any statistically significant difference in disease free and overall survivals between cisplatin plus 5-FU and cisplatin plus paclitaxel. There was over 10% difference in disease free survival between the two groups, but which did not reach statistical significance. If there is any survival difference between these two regimens, large prospective randomized controlled trials might be necessary to demonstrate such a difference. Given a similar survival outcome, less toxic chemotherapy is considered to be a better choice. For this purpose, the dosage of paclitaxel might be reduced, no additional chemotherapy after radiation might be employed, or paclitaxel might be excluded from the regimens of chemoradiation (i.e., cisplatin alone). This is based upon our observation that paclitaxel at a dose of 135 mg/m² for four cycles causes severe toxicity without any overall survival benefits. In particular, severe neutropenia can be lethal unless rapid recovery is not achieved. More importantly, paclitaxel is far more costly than 5-FU, such that the use of paclitaxel appears to be not cost-effective. A recent study also demonstrated that a regimen of weekly cisplatin alone in chemoradiation significantly improves treatment compliance and reduces acute hematologic toxicity, while not affecting response and survival rates.¹⁶ Since 2005, we have utilized more frequently a weekly regimen of cisplatin (40 mg/m² each cycle) for 6 weeks with concurrent radiation in patients than cispla-

tin combination regimen (CF or CP).

In conclusion, chemoradiation with cisplatin plus paclitaxel showed a more severe form of leukopenia, neutropenia, alopecia, hypersensitivity and peripheral neuropathy, but less gastrointestinal side effect, in particular nausea than that with cisplatin plus 5-FU in patients with locally advanced cervical carcinoma. However, there was no difference in survival outcome between these 2 regimens. Limitations of our present study include a retrospective study, a non-randomized controlled trial, and a study with a small sample size. Therefore, large prospective randomized controlled studies are needed to confirm this result.

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