Neoadjuvant chemotherapy followed by extended-field concurrent chemoradiotherapy in squamous cell carcinoma of the cervix with positive paraaortic lymph nodes: two cases

M. Hirakawa, *M.D.*; **Y. Nagai,** *M.D., Ph.D.*; **C. Yagi,** *M.D.*; **T. Nashiro,** *M.D.*; **M. Inamine,** *M.D., Ph.D.*; **Y. Aoki,** *M.D., Ph.D.*

Department of Obstetrics and Gynecology, Faculty of Medicine, University of the Ryukyus, Okinawa (Japan)

Summary

Purpose: To report the feasibility of neoadjuvant chemotherapy (NAC) followed by extended-field concurrent chemoradiotherapy (EF-CCRT) for squamous cell carcinoma of the cervix (CC) with paraaortic lymph node (PAN) metastasis. *Methods:* Two patients were diagnosed with CC with positive PAN, and received two courses of cisplatin (120 mg/m^2) in a neoadjuvant setting. They then received extended-field, external-beam radiotherapy (50.4 Gy) followed by intracavitary brachytherapy concurrently with cisplatin (20 mg/m^2 x 5 days) at 21-day intervals. *Results:* EF-CCRT was interrupted in one patient for five days because of grade 4 neutropenia. No severe late toxicities were observed. The two patients are alive with no evidence of recurrence at present. *Conclusions:* NAC followed by EF-CCRT is feasible and may improve the survival outcome of patients with CC with positive PAN.

Key words: Cervical cancer; Paraaortic lymph node metastasis; Neoadjuvant chemotherapy; Concurrent chemoradiotherapy.

Introduction

The survival outcome of patients diagnosed as having cervical cancer with paraaortic lymph node (PAN) metastasis is poor. Several retrospective studies have demonstrated a 5-year survival rate of approximately 30% in the patients treated with extended-field (EF) radiation therapy (RT) alone [1, 2]. To improve the survival outcome, cisplatin-based EF concurrent chemoradiation therapy (EF-CCRT) has been used to treat patients with cervical cancer with PAN metastasis. However, the survival rates at three to four years in these trials were reported to still be 30-39% [3, 4]. These trials emphasized that distant metastases were predominant sites of treatment failure. Ayman *et al*. [5] reported preliminary data showing that concurrent cisplatin-based chemotherapy with EFRT for this subset of patients appeared to improve pelvic and PAN control but not the rate of distant metastasis and survival. All patients in whom the cancer recurred died because of distant metastasis, which suggests that more effective systemic therapy should be explored.

To control distant failure, we treated patients with PAN metastasis using systemic neoadjuvant chemotherapy (NAC) followed by EF-CCRT. Here we present the preliminary report of two cases treated with NAC followed by EF-CCRT.

Materials and Methods

The characteristics of the patients are shown in Table 1. Both patients were diagnosed with International Federation of Gynaecology and Obstetrics (FIGO) Stage IIIb squamous cell carcinoma of the cervix with PAN metastasis (20 x 18 mm and 15 x 12 mm in size, respectively) evaluated by computed tomography (CT). Pelvic lymph node enlargement was also detected by CT (at least 10 mm in diameter). The patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and adequate hematologic, hepatic, and renal (creatinine clearance: ≥ 60 ml/min) functions. Written informed consent was obtained prior to treatment. Initially, two courses of 120 mg/m^2 of cisplatin (CDDP) was administered intravenously at 21-day intervals. Appropriate hydration and antiemetics were given before and after CDDP administration. We chose a dose of 120 mg/m^2 of CDDP for NAC because several studies have demonstrated that nephrotoxicity and peripheral neuropathy in response to this dose is acceptable [6]. After the completion of NAC, PAN shrinkage was observed. A combination of external-beam radiotherapy (EBRT) for five days per week, and high-dose-rate intracavitary brachytherapy (HDR-ICRT) using Ir-192 were delivered. The pelvic and paraaortic areas (EF) were treated as a continuous area, with a superior field border at the space between Th12 and L1. EF irradiation was delivered at a total dose of 45 Gy in 25 fractions, after which whole pelvic irradiation was delivered (5.4 Gy in 3 fractions). A midline block (4 cm width at the midline) was inserted into the center of the pelvic field after 39.6 Gy had been delivered. Boost EBRT was delivered to the enlarged pelvic nodes and infiltrated parametrium. A total dose of 6 Gy in three fractions was delivered. Three fractions of HDR-ICRT with a single dose of 6 Gy was delivered at point A once a week. Cisplatin (20 mg/m^2 for 5 days) was administered concomitantly with RT every 21 days [7]. Acute toxicity was graded according to NCI-CTC version 3.0. Late complications, such as

Revised manuscript accepted for publication July 30, 2007

Table 1. — *Patient characteristics*.

	Case 1	Case 2
Age (years)	63	50
Parity (G-P)	4-3	5-3
FIGO stage	IIIB	IIIB
Tumor size (cm)	4.2 x 3.8	5.0 x 3.7
PLN swelling	positive	positive
PAN swelling (mm)	20 x 18	15 x 12
SCCAg value (ng/ml)	1.9	2.0

Table 2. — *Acute toxicities of NAC and CCRT.*

Acute toxicities	Grade	Case 1 (grade)	Case 2 (grade)
NAC			
Hematological	White blood cells	1	1
	Hemoglobin	1	1
	Platelets	1	0
CCRT			
Hematological	White blood cells	4	3
	Hemoglobin	3	2
	Platelets	3	1
Non-hemoatological	GI[a)] (upper)	2	1
	GI (lower)	1	1
	Neurology	2	1
	Skin	0	0
	Genitourinary	0	0
	Liver	1	0

[a] Gastrointestinal toxicities.

Table 3. — *Summary of treatment*.

		Case 1	Case 2
Total dose of CDDP (mg/body)		608.5	485.0
Number of courses of CDDP in operation of CCRT		2	1
Reduction ratio of lymph nodes (%)	PAN	60	100
	Local	90	91
Interruption of radiation therapy (days)		5	0
Progression-free survival intervals (months)		22	15

proctitis, cystitis, and enterocolitis, were graded according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. Any symptoms defined in these schemes were considered to be treatment-related. These patients gave written informed consent before treatment.

Results

In case 1, NAC reduced PAN size by 60% and reduced the size of the local tumor by 90%. In case 2, PAN swelling disappeared and the cervical tumor shrank to 91% in size. A complete pathologic and clinical response was achieved in both patients at the time of completion of EF-CCRT. At 15 and 22 months of follow-up, respectively, the two patients were alive with no evidence of recurrence. The most severe toxicity experienced by the two patients is shown in Table 2. There were no treatment-related deaths and both patients experienced acute hematology. RT was interrupted in one patient for five days because of grade 4 neutropenia. No severe late complication associated with RT was observed. Case 1 experienced grade 2 peripheral neuropathy associated with chemotherapy.

Discussion

The incidence of positive PAN has been reported to be 6%, 16%, and 25% in patients with FIGO Stage I, II, and III disease, respectively [8]. Berman *et al*. [8] reported that the median survival of 98 patients with Stage IIB and IIIB cervical cancer (PAN metastases) treated with EFRT was 15.2 months and the 3-year survival was 25%. Grigsby *et al*. [3] reported that the 3-year and 5-year overall survival rates of 43 patients treated with EFRT were 37% and 32%, respectively. Forty percent (n = 17) of the patients developed distant metastasis with or without pelvic failure. Because of the poor prognosis of patients treated with EFRT alone, several studies using CCRT have been conducted. The GOG conducted a multicenter trial of CCRT to evaluate the feasibility of EFRT concurrent with 5-fluorouracil and cisplatin. The main grade 3/4 acute toxicities were gastrointestinal (18.6%) and hematologic (15.1%) in nature. Distant metastasis occurred in 41.9%, and pelvic failure was observed in 31.4% of the patients. The 3-year overall survival and progression-free survival were 39% and 34%, respectively [4]. Recently, Saad *et al*. [5] reported the treatment outcomes for cervical cancer patients with PAN treated with EFRT with or without chemotherapy. The median follow-up period was 26 months. The 3-year pelvic node and PAN control rate was 100% and 42.2%, respectively, (p = 0.03), and the 3-year distant control rate was 81.8% and 46.2% (p = 0.5) with and without chemotherapy, respectively. However, Saad et al. concluded that the addition of concurrent cisplatin-based chemotherapy to EFRT for this subset of patients appeared to improve the pelvic and PAN control rate but not the rate of distant metastasis and survival. All the patients with recurrent disease died as a result of distant metastasis, which suggests that a more effective systemic therapy should be explored.

Several studies have demonstrated the efficacy of NAC followed by CCRT for the treatment of head and neck cancer. These studies concluded that the treatment decreased distant metastasis by 20% and resulted in a better prognosis [9, 10]. In our patients, NAC was used for the control of distant metastasis in two PAN-positive patients with squamous cell carcinoma of the cervix. The adverse effect of NAC was mild, and there was no grade 3 or 4 toxicity. In contrast, the two patients had grade 3 neutropenia during EF-CCRT. However, the acute and late gastrointestinal toxicities of EF-CCRT were mild, and the patients completed their planned treatments. Because of the short follow-up intervals, the efficacy of NAC followed by CCRT is unclear; however, the patients were alive without recurrence for over a year. Due to its feasibility and potential efficacy, there is the possibility that NAC followed by CCRT may improve the prognosis of cervical cancer patients with positive PAN.

Conclusions

NAC followed by EF-CCRT is feasible and may improve the survival outcome of patients with CC with positive PAN.

References

[1] Grigsby P.W., Perez C.A., Chao K.S. *et al*.: "Radiation therapy for carcinoma of the cervix with biopsy-proven positive paraaortic lymph nodes". *Int*. *J*. *Radiat*. *Oncol*. *Biol*. *Phys*., 2001, *49,* 733.

[2] Vigliotte A.P., Wen B.C., Hussey D.H. *et al*.: "Extended field irradiation for carcinoma of the uterine cervix with positive periaortic nodes". *Int*. *J*. *Radiat*. *Oncol*. *Biol*. *Phys*., 1992, *23,* 501.

[3] Grigsby P.W., Heydon K., Mutch D.G. *et al*.: "Long-term follow-up of RTOG 92-10: cervical cancer with positive paraaortic lymph nodes". *Int*. *J*. *Radiat*. *Oncol*. *Biol*. *Phys*., 2001*, 51*, 982.

[4] Varia M.A., Bundy B.N., Deppe G. *et al*.: "Cervical carcinoma metastatic to paraaortic nodes: extended field radiation therapy with concomitant 5-fluorouracil and cisplatin chemotherapy: a Gynecologic Oncology Group study". *Int*. *J*. *Radiat*. *Oncol*. *Biol*. *Phys*., 1998, *42,* 1015.

[5] Saad A., Simon S. Lo, Ihn Han *et al*.: "Radiation therapy with or without chemotherapy for cervical cancer with periaortic lymph node metastasis". *Am*. *J*. *Clin*. *Oncol*., 2004, *27,* 256.

[6] Markman M., D'acquisto R., Iannotti N. *et al*.: "Phase-1 trial of high-dose intravenous cisplatin with simultaneous intravenous sodium thiosulfate". *J*. *Cancer Res*. *Clin*. *Oncol*., 1991, *117*, 151.

[7] Fields A.L.: "Mature results of a phase II trial of concomitant cisplatin/pelvic radiotherapy for locally advanced squamous cell carcinoma of the cervix". *Gynecol*. *Oncol*., 1996, *61,* 416.

[8] Berman M.L., Keys H., Creasman W. *et al*.: "Survival and patterns of recurrence in cervical cancer metastatic to periaortic lymph nodes (a Gynecologic Oncology Group study)". *Gynecol*. *Oncol*., 1984, *19,* 8.

[9] Paccagnella A. *et al*.: "Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: A study by the Gruppo di Studio sui Tumori della Testa e del Collo". *J*. *Natl*. *Cancer Inst*., 1994, *86,* 265.

[10] Department of Veterans Affairs Laryngeal Cancer Study Group: "Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer". *N*. *Engl*. *J*. *Med*., 1991, *324*, 1685.

Address reprint requests to:
M. HIRAKAWA, M.D.
Department of Obstetrics and Gynecology
Faculty of Medicine
University of the Ryukyus
207 Uehara Nishihara
Okinawa 903-0215 (Japan)
e-mail: h013916@med.u-ryukyu.ac.jp