Neoadjuvant intraarterial chemotherapy for stage IIB-IIIB cervical cancer in Japanese women

SHOJI KAKU[1], KENTARO TAKAHASHI[1], YOSHITAKA MURAKAMI[2], SHIROU WAKINOUE[1], TETSUYA NAKAGAWA[1], YOSHIHIKO SHIMIZU[1], NOBUYUKI KITA[1], YOICHI NODA[1] and TAKASHI MURAKAMI[1]

Departments of [1]Obstetrics and Gynecology, and [2]Medical Statistics, Shiga University of Medical Science, Otsu, Shiga 520-2192, Japan

Received April 6, 2010; Accepted May 31, 2010

DOI: 10.3892/etm_00000102

Abstract. Chemoradiotherapy is currently the main treatment for locally advanced cervical cancer, but neoadjuvant intraarterial chemotherapy (IA-NAC) has been reported to achieve favorable results. This study investigated the efficacy of several different IA-NAC regimens. The subjects were 55 patients with stage IIB-IIIB cervical cancer who received IA-NAC between January 1991 and April 2006. IA-NAC was administered for a total of 1-3 courses at 3-week intervals, with three different regimens being employed in chronological order. The response rate achieved with IA-NAC was 90.2% for squamous cell carcinoma, 60% for adenosquamous carcinoma and 42.9% for adenocarcinoma. Surgery was performed after IA-NAC in 36 patients, and radiotherapy alone was performed in 19 patients. The 5-year survival rate was 72.9% for patients with squamous cell carcinoma and 50% for those with adenocarcinoma or adenosquamous carcinoma. PAMF therapy (cisplatin, epirubicin, mitomycin-C and 5-fluorouracil) achieved a response rate of ≥90% for squamous cell carcinoma, as did CDDP + THP therapy (cisplatin plus pirarubicin), while PACF therapy (cisplatin, epirubicin, cyclophosphamide and 5-flurouracil) achieved a better response rate for adenosquamous carcinoma and adenocarcinoma. Grade 3 or 4 hematological toxicity was significantly more common with PAMF therapy. In conclusion, IA-NAC improved the survival of patients with squamous cell carcinoma. CDDP + THP therapy achieved a high response rate with little hematologic toxicity. PACF therapy achieved a significantly higher response rate in patients with adenosquamous carcinoma or adenocarcinoma. Therefore, IA-NAC may be a therapeutic option for locally advanced cervical cancer, particularly using the above-mentioned regimens.

Correspondence to: Dr Shoji Kaku, [3]*Present address*: Department of Obstetrics and Gynecology, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan
E-mail: kaku@med.kawasaki-m.ac.jp

Key words: cervical cancer, neoadjuvant intraarterial chemotherapy, survival rate, chemotherapy regimen

Introduction

Concurrent chemoradiotherapy (CCRT) is the main treatment for locally advanced cervical cancer (1-3). Neoadjuvant chemotherapy (NAC) was widely employed until CCRT became standard, and favorable results have been reported (4-6). However, the efficacy of NAC has not been confirmed by some researchers (7-11), therefore its value remains unclear. Neoadjuvant intraarterial chemotherapy (IA-NAC) is another method of delivering NAC as an alternative to systemic chemotherapy. IA-NAC has been reported to achieve beneficial results that cannot be obtained by systemic chemotherapy or CCRT (12-15), but conclusive evidence is limited, and a standard IA-NAC regimen has not been established. We have employed IA-NAC to treat advanced cervical cancer since 1991 and have used three regimens over that period. The results obtained with each of these regimens were examined in the present study.

Materials and methods

Patients. Between January 1991 and April 2006, 55 patients with stage IIB-IIIB primary cervical cancer were enrolled in the study. All patients gave their written informed consent to treatment. Eligibility criteria were as follows: age <75 years, no distant metastasis, WHO performance status of 0-2, no previous treatment and adequate renal, pulmonary, hepatic, bone marrow and cardiac function. The mean patient age was 53.5 years (range 28-74). Table I summarizes the FIGO clinical stage and tumor histology. There were 32 patients in FIGO stage IIB, 1 patient in stage IIIA and 22 patients in stage IIIB. There were 41 squamous cell carcinomas, 5 adenosquamous carcinomas, 7 adenocarcinomas and 2 other tumors.

Neoadjuvant intraarterial chemotherapy (IA-NAC). Angiography was performed to detect the tumor feeding vessels before IA-NAC. Catheters were inserted by the Seldinger's technique and were advanced into each of the uterine arteries superselectively, when possible. In the event difficulty was encountered in catheterizing either of the uterine arteries, the catheter tip was placed in the internal iliac artery instead. Anticancer agents were injected over

20-30 min. After treatment, the catheters were removed, and sandbags were placed to apply firm pressure to the groin for 6 h. Hydration with normal saline and 5% dextrose was started from 3 h before IA-NAC and was continued to maintain a urine output >100 ml/h for 24 h.

The following three different regimens were employed for IA-NAC in chronological order. i) Between January 1991 and December 1996, BMP therapy [bleomycin (20 mg), mitomycin-C (10 mg) and cisplatin (80 mg/m^2)] was administered to 12 patients. They included 9 patients with squamous cell carcinoma, 2 patients with adenosquamous carcinoma and 1 patient with adenocarcinoma. ii) Between January 1997 and March 2000, either of the following two regimens was administered depending on the tumor histology. PAMF therapy [cisplatin (80 mg/m^2), epirubicin hydrochloride (60 mg/m^2), mitomycin-C (20 mg) and 5-fluorouracil (500 mg)] was administered to 20 patients with squamous cell carcinoma and 2 patients with other histological types. PACF therapy [cisplatin (80 mg/m^2), epirubicin hydrochloride (60 mg/m^2), cyclophosphamide (500 mg) and 5-fluorouracil (500 mg)] was administered to 2 patients with adenosquamous carcinoma and 2 patients with adenocarcinoma. iii) Between April 2000 and April 2006, CDDP + THP therapy [cisplatin (100 mg/m^2) and pirarubicin hydrochloride (40 mg)] was administered to 12 patients with squamous cell carcinoma, 1 patient with adenosquamous carcinoma and 4 patients with adenocarcinoma.

IA-NAC was administered for 1-3 courses every 3 weeks. The number of courses given depended on the tumor response and operability determined by MRI and pelvic examination.

Assessment of response. The complete blood count and renal and liver function tests were performed before each course of IA-NAC. Tumor dimensions were measured by MRI before and after therapy. Patients were evaluated for tumor response according to the Response Evaluation Criteria in Solid Tumors (RECIST).

Additional therapy. Type III radical hysterectomy (16) with pelvic lymphadenectomy was performed in patients who responded to IA-NAC, when possible. Patients who did not respond to IA-NAC and could not tolerate or refused surgery received pelvic radiotherapy, including external irradiation (Linac 50.4 Gy) and brachytherapy delivered by a remote control afterloading system using 60Co (RALS 20-40 Gy). After radical hysterectomy, patients who had poor prognostic factors, including a positive resection margin, lymph node metastases, vessel invasion, parametrial infiltration and vaginal invasion, also received postoperative adjuvant radiation therapy (Linac 45-50.4 Gy).

Follow-up. After treatment, patients were reviewed every 3 months for 3 years, then every 6 months for the next 2 years and annually thereafter. At each follow-up visit, general and gynecologic examinations and cervical cytology were performed. Computed tomography and MRI were conducted once or twice a year. The median follow-up period for all the patients was 63.2 months (range 5-182).

Statistical analysis. Overall survival was defined as the time from the start of the first course of IA-NAC to death from any cause or to the date of last contact. The Kaplan-Meier method was used to describe overall survival, and the log-rank test was used to examine differences in survival between the different regimens. We initially examined the difference in survival between the squamous cell carcinoma group and the 'adenosquamous carcinoma + adenocarcinoma' group, after which survival with each anticancer regimen was subjected to analysis.

The Chi-square test was used for the comparison of the response rate and the hematological toxicity of each anticancer regimen. All statistical tests were performed two-sided, and P=0.05 was accepted as statistically significant.

Table I. FIGO stage and tumor histology of the eligible patients.

Stage	IIB	IIIA	IIIB	Total
Histology				
Squamous	23	1	17	41
Adenosquamous	4	0	1	5
Adeno	5	0	2	7
Others	0	0	2	2
Total	32	1	22	55

Squamous, squamous cell carcinoma; Adenosquamous, adenosquamous carcinoma; Adeno, adenocarcinoma; Others, other histological types.

Results

Number of courses. Eight of the 55 patients (14.5%) received 1 course of IA-NAC, 36 patients (65.5%) received 2 courses and 11 patients (20.0%) received 3 courses (mean 2.1).

Clinical response. The response rate achieved with IA-NAC was 90.2% for squamous cell carcinoma, 60% for adenosquamous carcinoma and 42.9% for adenocarcinoma, and a significant difference was observed between squamous cell carcinoma and the other histological types (P<0.01). Pathological CR (complete disappearance of the tumor confirmed by postoperative histological examination) was only achieved in 3 patients with squamous cell carcinoma, i.e., in 5.5% (3/55) of the entire study population.

Response rates were also compared between the different IA-NAC regimens. After excluding 2 patients with special tumors, the subjects were classified into 41 patients with squamous cell carcinoma and 12 patients with adenosquamous carcinoma or adenocarcinoma (Table II). In patients with squamous cell carcinoma, the response rate achieved with BMP, PAMF and CDDP + THP therapy was 77.8, 95 and 91.7%, respectively. The response rate was lower with BMP than with the other two regimens, but a significant difference was not observed (P=0.345). In patients with adenosquamous carcinoma or adenocarcinoma, the response rate achieved with BMP, PACF and CDDP + THP was 33.3, 100 and 25%, respectively. The response to PACF was significantly higher compared to the other two regimens (P=0.047), although the number of patients treated was small.

Table II. Response rate of squamous cell carcinoma or adenosquamous carcinoma + adenocarcinoma.

Histological type	Regimen	Total	CR	PR	SD	PD	Response rate (%)
Squamous (n=41)							
	BMP	9	2	5	2	0	77.8
	PAMF	20	6	13	1	0	95.0
	CDDP + THP	12	6	5	1	0	91.7
Ad. Sq + Ad (n=12)							
	BMP	3	0	1	2	0	33.3
	PACF	4	0	4	0	0	100.0
	CDDP + THP	5	0	1	4	0	25.0

Squamous, squamous cell carcinoma; Ad. Sq, adenosquamous carcinoma; Ad, adenocarcinoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table III. Hematological toxicity of each regimen.

Regimen	Parameter	Grade				
		0	1	2	3	4
BMP (n=12)						
	WBC	1	3	7	1	0
	Platelets	6	3	3	0	0
	Hemoglobin	0	1	10	1	0
PAMF (n=22)						
	WBC	0	0	3	13	6
	Platelets	4	3	5	9	1
	Hemoglobin	0	1	13	7	1
PACF (n=4)						
	WBC	0	0	2	2	0
	Platelets	4	0	0	0	0
	Hemoglobin	0	1	3	0	0
CDDP + THP (n=17)						
	WBC	2	2	8	5	0
	Platelets	15	2	0	0	0
	Hemoglobin	0	2	14	1	0

Other therapy. After IA-NAC, type III radical hysterectomy was performed in 81.3% (26/32) and 43.5% (10/22) of the patients with stage IIB and IIIB disease, respectively, and radical hysterectomy was performed in 65.5% (36/55) of the patients. Among the 36 patients who underwent surgery, radiotherapy was performed as postoperative adjuvant therapy in 28 patients. Patients who did not respond to IA-NAC or who refused surgery after IA-NAC and only received radiotherapy accounted for 34.5% (19/55) of the subjects.

Adverse events due to IA-NAC. Table III shows the hematological toxicity of each regimen. Adverse effects were evaluated using the National Cancer Institute – Common Toxicity Criteria (NCI-CTC) version 3.0. The data were collected retrospectively from the patient files.

Grade 3 and 4 toxicity was significantly more common with PAMF than with the other regimens for the WBC count, platelet count and hemoglobin ($P<0.01$, $P<0.01$ and $P<0.01$, respectively). With regard to nonhematological toxicities, renal and hepatic dysfunction caused by IA-NAC was never worse than grade 1.

Specific complications of IA-NAC included gluteal pain in 5 patients (9.1%), gluteal skin pigmentation in 2 patients (3.6%) and vesical necrosis in 2 patients (3.6%). Vesical necrosis occurred in 1 patient each after treatment with PAMF and CDDP + THP. The uterine artery was employed for superselective infusion in both patients, but a feeding vessel to the bladder could not be completely excluded by angiography at the time of treatment.

Survival. The survival rate was examined separately for patients with squamous cell carcinoma and for those with adenosquamous carcinoma or adenocarcinoma. The 5-year survival rate was 72.9% for patients with squamous cell carci-

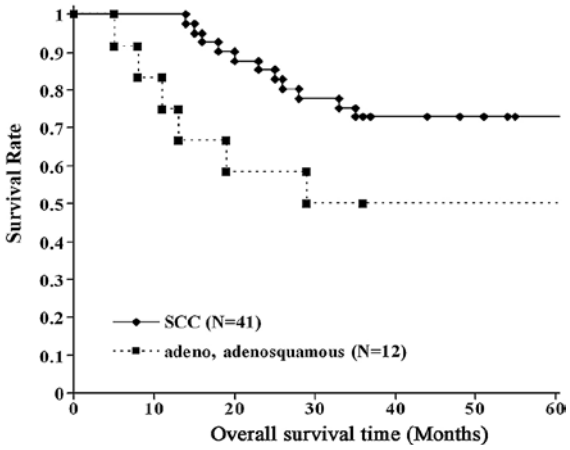

Figure 1. Kaplan-Meier estimates of overall survival for patients with squamous cell carcinoma or adenosquamous carcinoma and adenocarcinoma. The 5-year survival rate was 72.9% for patients with squamous cell carcinoma and 50% for patients with adenosquamous carcinoma or adenocarcinoma. SCC, squamous cell carcinoma; Adeno, adenocarcinoma.

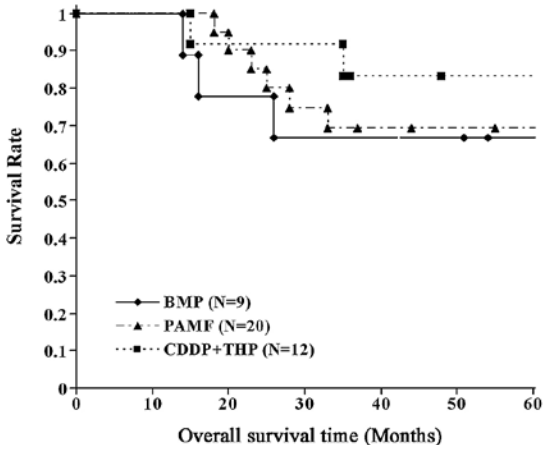

Figure 2. Kaplan-Meier estimates of overall survival for patients with squamous cell carcinoma who received BMP, PAMF or CDDP + THP therapy. The 5-year survival rate was 66.7% with BMP, 69.3% with PAMF and 83.3% with CDDP + THP therapy.

noma and 50% for patients with adenosquamous carcinoma or adenocarcinoma. Although survival was more favorable in the squamous cell carcinoma group, the difference was not significant (P=0.056) (Fig. 1).

When the survival achieved with each anticancer regimen was examined, the 5-year survival rate of patients with squamous cell carcinoma was 66.7% with BMP, 69.3% with PAMF and 83.3% with CDDP + THP therapy. Thus, CDDP + THP therapy was the most effective, although the difference was not significant compared to the other two regimens (P=0.337) (Fig. 2). In patients with adenosquamous carcinoma or adenocarcinoma, the 5-year survival rate was 33.3% with BMP, 75% with PACF and 20% with CDDP + THP therapy. PACF therapy was the most effective, although the difference in outcome compared with the other two regimens was not significant (P=0.184) (Fig. 3).

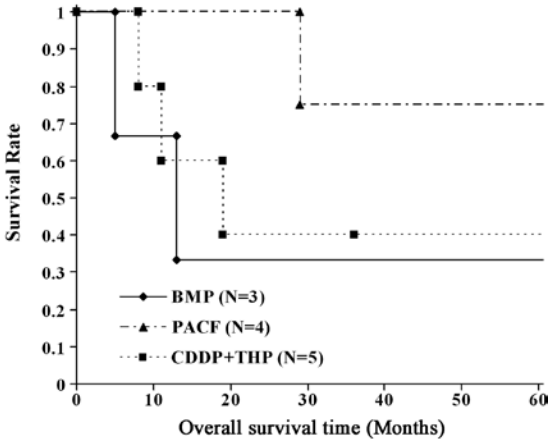

Figure 3. Kaplan-Meier estimates of overall survival for patients with adenosquamous carcinoma or adenocarcinoma who received BMP, PACF or CDDP + THP therapy. The 5-year survival rate was 33.3% with BMP, 75% with PACF and 20% with CDDP + THP therapy.

Discussion

NAC was commonly employed for cervical cancer until CCRT became a standard treatment, and favorable results have been obtained (4-6). However, the efficacy of NAC has not been confirmed (7). There have also been negative reports concerning the efficacy of NAC for advanced cervical cancer (stage III or IV) (8-11), therefore its value remains controversial.

IA-NAC is employed to obtain higher tissue drug concentrations by direct infusion of anticancer agents into the feeding artery of a tumor to maximize the anticancer activity and minimize adverse effects related to drugs entering the systemic circulation. The first report on IA-NAC was published in 1950 by Bierman *et al* (17), and its use in the gynecological field was reported by Cromer *et al* in 1952 (18). One of the reasons for the lack of popularity of IA-NAC is presumed to be the need for special procedures, such as arterial catheterization. The fact that there are no prospective studies providing conclusive evidence may be another reason, but favorable results that are unlikely to be achieved with systemic chemotherapy or CCRT have been reported (12-15).

The present study revealed that the response rate of squamous cell carcinoma to IA-NAC was very high at 90.2%. Investigation of survival also showed a high 5-year survival rate of 72.9% in patients with stage IIB-IIIB squamous cell carcinoma, which was improved compared to the previously reported results for chemoradiation (19). A standard IA-NAC regimen has not been established and the use of various anticancer agents has been reported (12-15). We compared three IA-NAC regimens that were employed in chronological order. In the patients with squamous cell carcinoma, PAMF and CDDP + THP therapy achieved a response rate of ≥90%. The 5-year survival rate achieved by CDDP + THP therapy was higher than those for BMP or PAMF therapy, although significant differences were not observed (P=0.337) (Fig. 2), and the hematological toxicity of CDDP + THP therapy was significantly less severe than that of PAMF therapy (Table III). This suggests that it would be reasonable to use CDDP + THP therapy. On the other hand, studies of systemic chemotherapy for adenocarcinoma of the cervix have shown that the response rate of advanced or recurrent cancer to NAC ranges

between 20 and 50% (20-22), and is relatively low (50-80%) even for early stage cancer (23-25). In our study of IA-NAC, the response rate of adenosquamous carcinoma and adenocarcinoma was 60 and 42.9%, respectively, and these rates were significantly lower than that for squamous cell carcinoma. All 4 patients that were administered PACF therapy achieved a partial response, and 3 of them achieved 5-year survival. However, the number of patients treated was small, therefore the efficacy of PACF therapy should be further investigated.

Vesical necrosis occurred in 2 patients as a specific adverse effect of intraarterial therapy and it was considered to be attributable to high concentrations of anticancer agents reaching the bladder after superselective infusion into the uterine artery. When the presence of a feeding vessel for the bladder cannot be excluded by angiography before IA-NAC, the internal iliac artery should be selected instead for intraarterial infusion.

In conclusion, our study showed a high response rate and a high 5-year survival rate in patients with stage IIB-IIIB squamous cell carcinoma. Therefore, IA-NAC seems to be a reasonable treatment option for such tumors, and CDDP + THP therapy seems to be the most effective of the regimens we tested. Even in patients with stage IIB-IIIB adenosquamous carcinoma or adenocarcinoma, a 5-year survival rate of 50% was obtained. However, the number of patients treated was small, therefore the efficacy of PACF therapy should be further investigated.

References

1. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, Clarke-Pearson DL and Insalaco S: Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 340: 1144-1153, 1999.
2. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, Rotman M, Gershenson DM and Mutch DG: Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 340: 1137-1143, 1999.
3. Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler WC Jr, Clarke-Pearson DL and Liao SY: Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol 17: 1339-1348, 1999.
4. Sardi JE, Giaroli A, Sananes C, Ferreira M, Soderini A, Bermudez A, Snaidas L, Vighi S, Gomez Rueda N and di Paola G: Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage Ib squamous carcinoma of the cervix: the final results. Gynecol Oncol 67: 61-69, 1997.
5. Benedetti-Panici P, Greggi S, Colombo A, Amoroso M, Smaniotto D, Giannarelli D, Amunni G, Raspagliesi F, Zola P, Mangioni C and Landoni F: Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: results from the Italian multicenter randomized study. J Clin Oncol 20: 179-188, 2002.
6. Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-analysis Collaboration: Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient data from 21 randomised trials. Eur J Cancer 39: 2470-2486, 2003.
7. Chang TC, Lai CH, Hong JH, Hsueh S, Huang KG, Chou HH, Tseng CJ, Tsai CS, Chang JT, Lin CT, Chang HH, Chao PJ, Ng KK, Tang SG and Soong YK: Randomized trial of neoadjuvant cisplatin, vincristine, bleomycin, and radical hysterectomy versus radiation therapy for bulky stage IB and IIA cervical cancer. J Clin Oncol 18: 1740-1747, 2000.
8. Kumar L, Kaushal R, Nandy M, Biswal BM, Kumar S, Kriplani A, Singh R, Rath GK and Kochupillai V: Chemotherapy followed by radiotherapy versus radiotherapy alone in locally advanced cervical cancer: a randomized study. Gynecol Oncol 54: 307-315, 1994.
9. Sundfor K, Trope CG, Hogberg T, Onsrud M, Koern J, Simonsen E, Bertelsen K and Westberg R: Radiotherapy and neoadjuvant chemotherapy for cervical carcinoma. A randomized multicenter study of sequential cisplatin and 5-fluorouracil and radiotherapy in advanced cervical carcinoma stage 3B and 4A. Cancer 77: 2371-2378, 1996.
10. Souhami L, Gil RA, Allan SE, Canary PC, Araujo CM, Pinto LH and Silveira TR: A randomized trial of chemotherapy followed by pelvic radiation therapy in stage IIIB carcinoma of the cervix. J Clin Oncol 9: 970-977, 1991.
11. Tattersall MH, Lorvidhaya V, Vootiprux V, *et al*: Randomized trial of epirubicin and cisplatin chemotherapy followed by pelvic radiation in locally advanced cervical cancer. Cervical Cancer Study Group of the Asian Oceanian Clinical Oncology Association. J Clin Oncol 13: 444-451, 1995.
12. Park SY, Kim BG, Kim JH, Lee JH, Lee ED, Lee KH, Park KB, Lee BH and Kim KH: Phase I/II study of neoadjuvant intraarterial chemotherapy with mitomycin-C, vincristine, and cisplatin in patients with stage IIb bulky cervical carcinoma. Cancer 76: 814-823, 1995.
13. Scarabelli C, Zarrelli A, Gallo A and Visentin MC: Multimodal treatment with neoadjuvant intraarterial chemotherapy and radical surgery in patients with stage IIIB-IVA cervical cancer. A preliminary study. Cancer 76: 1019-1026, 1995.
14. Sugiyama T, Nishida T, Hasuo Y, Fujiyoshi K and Yakushiji M: Neoadjuvant intraarterial chemotherapy followed by radical hysterectomy and/or radiotherapy for locally advanced cervical cancer. Gynecol Oncol 69: 130-136, 1998.
15. Yamakawa Y, Fujimura M, Hidaka T, Hori S and Saito S: Neoadjuvant intraarterial infusion chemotherapy in patients with stage IB2-IIIB cervical cancer. Gynecol Oncol 77: 264-270, 2000.
16. Piver MS, Rutledge F and Smith JP: Five classes of extended hysterectomy for women with cervical cancer. Obstet Gynecol 44: 265-272, 1974.
17. Bierman HR, Byron RL Jr, Miller ER and Shimkin MB: Effects of intra-arterial administration of nitrogen mustard. Am J Med 8: 535, 1950.
18. Cromer JK, Bateman JC, Berry GN, Kennelly JM, Klopp CT and Platt LI: Use of intra-arterial nitrogen mustard therapy in the treatment of cervical and vaginal cancer. Am J Obstet Gynecol 63: 538-548, 1952.
19. Toita T, Moromizato H, Ogawa K, Kakinohana Y, Maehama T, Kanazawa K and Murayama S: Concurrent chemoradiotherapy using high-dose-rate intracavitary brachytherapy for uterine cervical cancer. Gynecol Oncol 96: 665-670, 2005.
20. Umesaki N, Fujii T, Nishimura R, Tanaka T, Nishida M, Fushiki H, Takizawa K, Yamamoto K, Hasegawa K and Izumi R: Phase II study of irinotecan combined with mitomycin-C for advanced or recurrent squamous cell carcinoma of the uterine cervix: the JGOG study. Gynecol Oncol 95: 127-132, 2004.
21. Dimopoulos MA, Papadimitriou CA, Sarris K, Aravantinos G, Kalofonos C, Gika D, Gourgoulis GM, Efstathiou E, Skarlos D and Bafaloukos D: Combination of ifosfamide, paclitaxel, and cisplatin for the treatment of metastatic and recurrent carcinoma of the uterine cervix: a phase II study of the Hellenic Cooperative Oncology Group. Gynecol Oncol 85: 476-482, 2002.
22. Papadimitriou CA, Sarris K, Moulopoulos LA, Fountzilas G, Anagnostopoulos A, Voulgaris Z, Gika D, Giannakoulis N, Diakomanolis E and Dimopoulos MA: Phase II trial of paclitaxel and cisplatin in metastatic and recurrent carcinoma of the uterine cervix. J Clin Oncol 17: 761-766, 1999.
23. Iwasaka T, Fukuda K, Hara K, Yokoyama M, Nakao Y, Uchiyama M and Sugimori H: Neoadjuvant chemotherapy with mitomycin C, etoposide, and cisplatin for adenocarcinoma of the cervix. Gynecol Oncol 70: 236-240, 1998.
24. Lissoni A, Gabriele A, Gorga G, Tumolo S, Landoni F, Mangioni C and Sessa C: Cisplatin-, epirubicin- and paclitaxel-containing chemotherapy in uterine adenocarcinoma. Ann Oncol 8: 969-972, 1997.
25. Benedetti-Panici P, Greggi S, Scambia G, Salerno MG, Amoroso M, Maneschi F, Cutillo G, Caruso A, Capelli A and Mancuso S: Locally advanced cervical adenocarcinoma: is there a place for chemo-surgical treatment? Gynecol Oncol 61: 44-49, 1996.