
GYNAECOLOGY

Randomized Trial of Intrabifurcation of Aorta Infusion by Mitomycin- C versus Mitomycin-C Plus Cisplatinum for Treatment of Squamous Cell Carcinoma of the Cervix Stage II-III

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ABSTRACT

Objective To compare the efficacy of intrabifurcation of aorta infusion by mitomycin- C (arm A) and mitomycin-C plus cisplatinum (arm B) as a neoadjuvant therapy to surgery or radiotherapy in squamous cell carcinoma of the cervix stage II-III.

Design Randomized trial.

Setting Gynaecological Oncology Division, Department of Obstetrics and Gynaecology, Siriraj Hospital, Mahidol University.

Subjects Sixty patients of cervical squamous cell carcinoma stage II-III who refused the standard radiation therapy were recruited between February 1987- December 1992.

Main outcome measures Response rate, drug toxicities, recurrent rate, 5-years survival.

Results The evaluable patients included 30 cases of each arm. Arm-A achieved the response rate of 96.7% with clinical complete response of 66.7%, where as 100.0% and 83.3% response rate in arm-B ($P > 0.05$), the pathological complete response rate was 50.0% and 60.0% in arm A and B respectively ($P > 0.05$). The recurrence or metastases of responders after surgery and adjuvant treatment was found in 17.2%

in arm-A, and 13.3% of arm-B ($p > 0.05$). The overall 5-years survival of both arms were similar (90.0%). The drugs toxicities were tolerable.

Conclusion The neoadjuvant chemosurgical single dose intrabifurcation of aorta infusion either mitomycin-C alone or mitomycin-C plus cisplatinum in the treatment of cervical squamous cell carcinoma stage II-III showed no significant difference in response rate, toxicities, recurrence, and overall 5-years survival.

Key words : intrabifurcation of aorta infusion, mitomycin-C versus mitomycin-C plus cisplatinum, cervical carcinoma

Cervical cancer is the most common cancer which shares three-fourths of all genital cancer in Thai women. Approximately half of the cervical cancer patients present as clinical stage II-IV.^(1,2) Radiation is currently accepted as a standard treatment. However many of these patients refused treatment and searched for traditional treatment such as herbs and superstitious treatment.

The neoadjuvant chemotherapy followed by surgery aiming to downgrade tumour may be another option. Mitomycin-C has antitumour activity against these squamous cell carcinoma and many reports yielded response rate of 22-85%.⁽³⁻⁸⁾ Our previous intravenous high dose mitomycin-C trial yielded a clinical complete response rate 16% and partial response rate of 68% with substantial toxicities.⁽⁹⁾ The single high dose mitomycin-C intrabifurcation of aorta infusion in the treatment of squamous cell carcinoma of the cervix stage II-III showed the response rate of 91.7% with the clinical complete response rate of 86.1%, the pathological complete response rate of 39.3%, the 5-years survival rate of the pathological complete response group was 100.0% and 88.2% for the residual cancer group with overall 5-years survival rate of 75%.⁽¹⁰⁾ The combination of mitomycin-C and cisplatinum in the treatment of recurrent, metastatic, or residual uterine cervical cancer post radiation yielded a complete response rate of 40% and partial response rate of 20%.⁽¹¹⁾

The objective of this study is to compare the efficacy of mitomycin-C and mitomycin-C plus cisplatinum as a neoadjuvant single dose intrabifurcation of aorta infusion.

Materials and Methods

Patient selection : Eligibility criteria included the histological proof of the cervical squamous cell carcinoma stage II-III, who refused radiation therapy during February 1987- December 1992. The age should not exceed 60 years. The size of the lesion was recorded based on clinical pelvic examination. No prior chemotherapy, no medical or psychological disease which precluded surgery. Patients had adequate bone marrow function (haemoglobin level greater than 8 g/dL, leukocyte count greater than 4,000/cu.mm., platelet count greater than 100,000/cu.mm.), normal liver function (serum SGOT level less than 100 sigma unit), normal renal function (serum creatinine level less than 2 mg/dL), and signed the consent form.

Randomisation : Computer-generated randomization.

Treatment plan : Patients were randomised to receive either a single dosage of mitomycin-C 35 mg/m² or mitomycin-C 30 mg/m² plus cisplatinum 50 mg/m², administered by intrabifurcation of aorta infusion over 5 minutes under fluorography. The technique included the compression of the femoral arteries just below the point of puncture during infusion. All patient were

admitted and monitored for at least 12 hours for observation of immediate complication. Nausea and vomiting was managed by dexamethasone 20 mg intravenously, and metoclopramide 10 mg subcutaneously with hydration prior to chemotherapy.

Response assessment and further treatment : The follow up included weekly physical examination, complete blood count, and non-haematologic toxicities based on WHO criteria. The evaluation of response was performed at 4 weeks after chemotherapy. The clinical complete response was defined as disappearance of cervical lesions, vaginal and parametrial involvement. Partial response was defined as a decrease of lesion at least 50%. Reduction of lesion less than 50% was defined as no response.

The patients who had complete or partial response with no parametrial involvement were treated by radical hysterectomy and pelvic lymphadenectomy. Radiotherapy was offered to ones who failed treatment or inoperable. The patient of no residual cancer in the surgical specimen was defined as the pathological complete response and residual cancer in the cervix were treated by oral mitomycin-C 2 mg/day x 7 days and 5-fluorouracil 200 mg/day x 7 days every 4 weeks for 6 cycles. The case of positive cancer in the pelvic lymph nodes was treated by external radiation 5000 cGy.

Statistical analysis : The comparison for response rate between the two arms was determined by Chi-square test. The comparison for recurrence or metastases, and significant toxicities was determined by Fisher exact test. Kaplan and Meier's method were used to estimate and compare survival.

Results

During February 1987-1992, 60 cases were enrolled into the trial. Each arm had 30 patients and were eligible and evaluable. Patient characteristics and response rate are summarized in Table 1. There were no significant difference in age and stage between the two arms of the study. Arm-A (mitomycin-C alone) had the response rate of 96.7% with clinical complete response 66.7%, where as 100.0% and 83.3% in arm-B (mitomycin-C plus cisplatinum), $P > 0.05$.

The significant toxicities are shown in Table 2. The difference was found only in leukopenia grade 3, 30.0% of arm-A and 6.7% of arm-B ($P < 0.05$).

Radical hysterectomy and pelvic lymphadenectomy were performed if there were evidence of response, arm-A 28 cases and 30 cases of arm-B. The pathological complete response occurred 10 out of 20 cases (50%) in arm-A and 10 out of 25 (60%) in arm-B ($P > 0.05$). A non-responder of arm-A refused radiation therapy, expired within 6 months. One partial responder of arm-A was treated by standard radiotherapy, the other one of this group showed positive pelvic nodes received the adjuvant external radiation, both of them were alive without disease. None of the patients in arm-B received the adjuvant radiotherapy.

The recurrence or metastases of responders after surgery and adjuvant treatment was found 5 of 29 cases (17.2%) in arm-A and 4 of 30 (13.3%) in arm-B ($P > 0.05$). The recurrence occurred in 7.5-25.5 months and 17.0-97.0 months respectively. These patients were treated by mitomycin-C plus cisplatinum intravenously and/or external radiation, 2 of arm-A expired at 10 and 37 months, 2 cases of arm-B expired at 28.5 and 51.5 months later.

The overall survival time (Fig. 1) in both

Table 1. The single intrabifurcation of aorta infusion by mitomycin-C (MMC) compared with combined mitomycin-C and cisplatinium (CDDP)

		Arm-A MMC n = 30	Arm-B MMC + CDDP n = 30	P- Value
1. Age	Range	26-60	29-60	NS
	Median	48.00	47.00	NS
2. Stage	IIA	2	2	-
	IIB	25	24	NS
	IIIB	3	4	-
3. Response	Clinical CR	20 (66.7%)	25 (83.3%)	NS
	PR	9 (30.0%)	5 (16.7%)	NS
	NR	1 (3.3%)	0	-
4. After radical hysterectomy and pelvic lymphadenectomy of clinical CR cases ;	Pathological CR	10/20 (50.0%)	15/25 (60.0%)	NS
5. Recurrence or metastases of responders after complete treatment ;		5/29 (17.2%)	4/30 (13.3%)	NS

CR - complete response ; PR - partial response ; NR - no response

Table 2. The significant toxicity of MMC compared with combined MMC and CDDP

		MMC n = 30	MMC + CDDP n = 30	P-Value
1. Haematological	Haemoglobin grade 3 (< 8 g/dL)	4 (13.3%)	0	-
	Leukocytes grade 3 (< 2000/mm ³)	9 (30.0%)	2 (6.7%)	< 0.05
	Platelets grade 4 (< 25000/mm ³)	2 (6.7%)	1 (3.3%)	NS
2. Gastrointestinal	Nausea/vomiting grade 3 (requiring therapy)	11 (36.7%)	17 (56.7%)	NS
	SGOT > 100	0	0	-
	Colitis	2 (6.7%)	0	-
3. Renal	Blood creatinine > 2 mg/dL	0	0	-
4. Hair loss grade 1-2		21 (70.0%)	24 (72.0%)	NS
5. Infection, positive haemoculture		2 (6.7%)	0	-
6. Hyperpigmentation of skin		3 (10.0%)	4 (13.3%)	NS

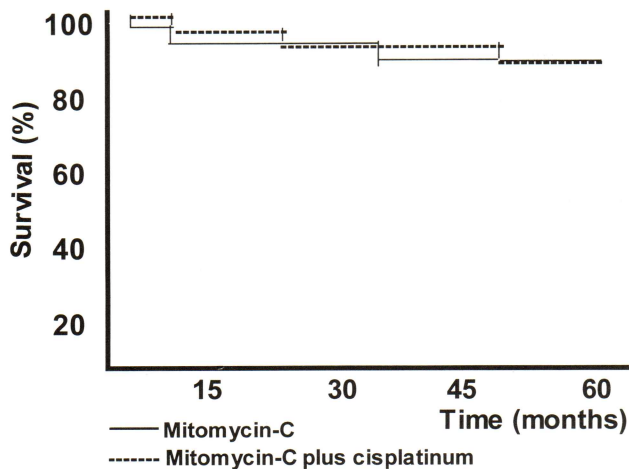


Fig. 1. Survival curve of the patients.

arms were comparable. The pathological complete responders of both arms achieved the 5 years survival 100%, but 70% for residual cancer group.

Discussion

The neoadjuvant chemosurgery of the two arms showed no significant statistical difference in the clinical complete response, pathological complete response and recurrence of the responders. This additional cisplatinum 50 mg/m² had no renal toxicity and low incidence of leukopenia grade 3, may be slightly low dose, cisplatinum could increase to 70 mg/m² for better results. However, either mitomycin-C 35 mg/m² or mitomycin-C 30 mg/m² plus cisplatinum 50 mg/m² achieved the satisfied results of 5 years survival for complete pathological response of 100% and 70% for residual cancer group. The overall 5-years survival of each group was 90%, comparing our previous trial of 75%.⁽¹⁰⁾ These procedures should be another alternative treatment for the patients, who refused the standard treatment.

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