Efficacy of the High Dose Mitomycin-C Intrabifurcation of Aorta Infusion for Treatment of Squamous Cell Carcinoma of Cervix Stage II B - III B

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Abstract : *The neoadjuvant single high dose chemotherapy for induction the high clinical complete regression with low toxicities, following by radical hysterectomy and pelvic lymphadenectomy produced high pathological complete regression and favourable survival time. This procedure was used instead of standard radiotherapy in treatment of squamous cell carcinoma of the uterine cervix stage II B -III B who refused the radiation treatment.*

The intrabifurcation of aorta by Mitomycin-C 35 mg/m2 single infusion was performed in 36 new cases, revealed the clinical complete regression 86.1% and partial regression 5.6% after chemotherapy 4-6 weeks. Twenty eight patients with clinical complete regression were treated by radical hysterectomy and pelvic nodes dissection, which showed pathological complete regression in 39.3%, small residual cancer in the cervix encountered in 39.3% and residual cancer in the cervix and/or positive pelvic nodes accounted for 21.4%. The bone marrow was moderately depressed in the second week after treatment but experiencing tolerable non-haematolgic toxic effects.

The recurrence rate occured 25.0% after radical surgery and oral chemotherapy. The over all 5-years survival rate was 75.0%. The follow up period until August 1992 showed that the survival time ranged from 6.5-101.5 months (median 93.5 months). The 5-years survival rate of the pathological complete regression group was 100.0%, and 88.2% for the residual cancer group. (Thai J Obstet Gynaecol 1994;6:1-6.)

Key words : intrabifurcation of aorta infusion, mitomycin-C, squamous cell carcinoma, radical hysterectomy

Short title : Mitomycin-C for cervical cancer stage II-III

The cervical cancer is the first most common gynaeclogic cancer, during 1980-1989 our department had the incidence of the cervical cancer 73% of the female genital cancer, approximately 57% of the patients fall into stage III-IV,[1] and the treatment should be radiation therapy. The numerous patients of this group were treated by herb or superstitions, instead of radiation therapy, thus had no chance of survival. The other alternative treatment such as neoadjuvant chemotherapy with surgery should be useful for these cases. The use of Mitomycin-C in treatment of advanced cervical cancer showed response rate of 22-85%.[2-6] The previous trial intravenous high dose Mitomycin-C in treatment of the cervical cancer stage II-III revealed the clinical complete regression 16% and partial regression 68%, with high incidence of toxicities.[7] The objective of this study was to find out the other model neoadjuvant chemotherapy with low incidence of toxicities, while producing the high clinical and pathological complete regression with favourable survival. The neoadjuvant single high dose Mitomycin-C intrabifurcation of aorta by infusion was performed in this trial.

Materials and Methods

The patients eligibility for study included the pathological finding of squamous cell carcinoma stage II B - III B, who refused of radiotherapy during March 1984 - February 1986. The size of the lesion should be measurable, having never been treated by other chemotherapy, and no medical or psychological disease which contraindicate for radical surgery. Patients were required to have adequate bone marrow function (a leukocyte count greater than 400/Cu.mm., a platelet count greater than 100,000/Cu.mm., haemoglobin level greater than 8 gm/100 ml., normal liver function (serum SGOT level more than 100 sigma unit, normal renal function (serum creatinine level less than 2 mg/100 ml.), and signed the consent form.

A single dosage of Mitomycin-C 35 mg/m2 was given intrabifurcation of aorta infusion over 5 minutes under fluorography with compression the femoral arteries just below the point of puncture. The patient was admitted in hospital at least 12 hours for observation of complication. Nausea and vomiting were treated by metoclopamide 10 mg. subcutaneously or intravenously every 4-6 hours.

The follow up included weekly physical examination, complete blood count, and non-haematologic toxicities observation. The evaluation of response was performed 4-6 weeks after medication. The clinical complete regression was defined as disappearance of lesion in the cervix, vaginal fornices and parametrium. Partial regression was defined as a decrease of lesion at least 50%. Decreasing of lesion less than 50% was defined as no regression.

The patients with complete

regression were treated by radical hysterectomy and pelvic lymph node dissection. The patient who had no residual cancer in the surgical specimen, was defined as the pathological complete regression, was treated postoperatively by oral Mitomycin-C 2 mg/day for 7 days in every 4 weeks for 6 cycles. The patient who had residual cancer in the cervix was treated postoperatively by the same dosage of the oral Mitomycin-C. The group of residual cancer in the cervix and/or positive cancer in the pelvic lymph nodes was treated by external radiation 5000 cGy.

Results

During March 1984-February 1986, 36 patients included in this trial, age ranged were 25-61 years (mean 44.8 ± 9.2). The majority of cases fell in 40-49 years old. The stage II B disease 28 cases age ranged between 26-61 years (mean 43.9 ± 8.3) and stage III B 8 cases age ranged between 25-60 years. (mean 47.8 ± 11.9)

Among 28 patients in stage II B, showed clinical complete regression 92.9%. The stage III B 8 patients have clinical complete regression

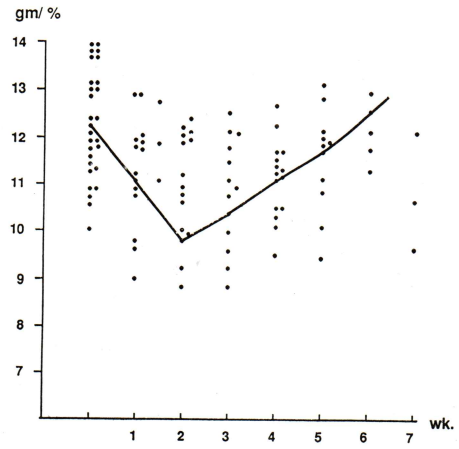

Fig. 1 Haemoglobin levels after mitomycin-C

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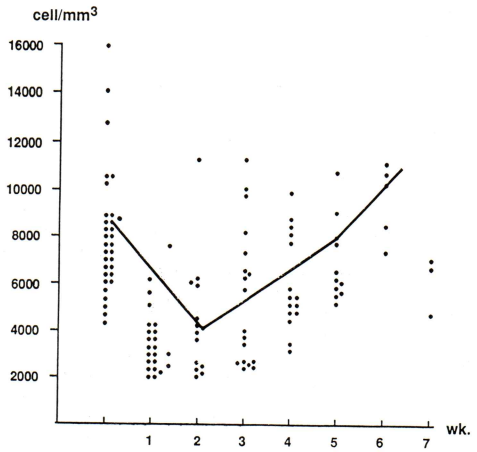

Fig. 2 Leucocyte count levels after mitomycin-C

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Table 1 ***Clinical response after Mitomycin-C infusion***

Stages	No.of patients	Response (%)		
		Complete regression	Partial regression	No regression
II	28	26 (92.9)	-	2 (7.11)
III	8	5 (62.5)	2 (25.0)	1 (12.5)
Total	36	31 (86.1)	2 (5.6)	3 (8.3)

Table 2 *Pathological finding after radical hysterectomy and pelvic lymphadenectomy in 28 cases of clinical complete regression*

Pathology report	Stage II	Stage III	Percentage (%)
No residual cancer	10	1	11 (39.3)
Residual cancer in cervix	10	1	11 (39.3)
Residual cancer in cervix and/or pelvic lymph nodes	5	1	6 (21.4)
Total	25	3	28

Table 3 *Recurrence after radical hysterectomy and pelvic lymphadenectomy in 28 cases of clinical complete regression group*

Stage	Pathological finding			Total
	Pathological Complete regression	Residual cancer in cervix	Residual cancer in cervix and or nodes	
II B	2	2	2	6
III B	-	-	1	1
	2	2	3	7

62.5%, and partial regression 25.0%. All of them have clinical complete regression 86.1%, and partial regression 5.6%. (Table 1)

The drug toxicity revealed moderate degree of marrow suppression at the end of the second week (Fig. 1,2). Two patients have leukocyte count grade 2 and 3, and spontaneously increased to the normal level in 4 weeks. The non-haematologic toxic effects revealed nausea-vomiting grade 2 69.44%, alopecia grade 2 47.22%, and blue nail 25.0%.

The radical hysterectomy and pelvic lymphadenectomy were performed in 28 patients of clinical complete regression group and revealed the pathological complete regression 39.1%, small residual cancer in the cervix 39.1%, small residual cancer in the cervix and/or positive pelvic lymph nodes 21.4% (Table 2). Three patients of clinical complete regression refused surgery, were treated by oral Mitomycin-C. One of them was alive without disease with survival time 101 months, 2 patients showed central recurrence or left supraclavicular node metastases within 7, 12 months and expired with survival time 12, 17 months.

The partial regression group was treated by oral Mitomycin-C, expired with survival time 6.5 and 8.0 months. No regression 3 cases, one

was treated by oral Mitomycin-C and two refused further treatment and expire with survival time 10, 8 and 7 months.

Seven of 28 patients (25.0%) in clinical complete regression group showed recurrence or distant metastases after radical surgery 9.0-37.0 months (Table 3). All of them were treated by external radiation or Bleomycin plus Mitomycin-C. Two of this group expired with survival time 22.5 and 27.5 months.

The over all 5-years survival was 27 out of 36 cases (75.0 %). The follow up was performed until August 1992, revealed survival time 6.5-101.5 months, median survival 93.5 months. The 5-years survival of the pathological complete regression was 100.0 %, and 88.2 % for the group of residual cancer in the cervix and or positive pelvic lymph nodes.

Discussion

The effectiveness of Mitomycin-C in treatment of the cervical cancer should be high dosage,[2-6] but not more than 40 mg/m2.[8] The multiple high dosage showed severe toxicities either haematologic or non-haematologic effect.[7] The single high dose intrabifurcation of arota infusion have the high concentration of drug in the pelvic organ especially cervix, uterus, pelvic wall including pelvic nodes. Thus we can increase the clinical complete regression to 86.1% comparing with our previous trial 16.0 %,[7] followed by a chance of radical surgery. Only the single infusion of chemotherapy in this trial induced the low and tolerable toxicities. Although the recurrence was found 25.0 % of cases post radical surgery and oral chemotherapy, we can treat with radiation or chemotherapy, unfortunately 2 patients did not response. In the future we can increase the oral Mitomycin-C to 3 mg/day for 7 days in combination with oral 5-Fluorouracil 300 mg/day for 7 days, however this recurrent rate may be decrease.

Conclusion

This procedure is the other alternative treatment for the patient of cancer stage II-III, who refused the standard radiation and we can preserve the ovarian function in young women. The 5-years survival of the patients after radical surgery reached 92.9 %, especially 100 % in the pathological complete regression group, and 88.2 % of the residual cancer group.

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