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Neoadjuvant Chemotherapy in Advanced Vulvar Cancer: A pilot study

Prasit Pengsaa
Banchong Udomthavornsuk
Thawalwong Ratanasiri
Vitaya Thithapandha

Division of Gynecologic Oncology,
Department of Obstetrics and Gynecology,
Faculty of Medicine, Khon Kaen University.

เคมีบำบัดก่อนผ่าตัดในมะเร็งปากช่องคลอดระยะลุกลาม : การศึกษานำ

ประสิทธิ์ เพ็งสา, บรรจง อุดมถาวรสุข, ถวัลย์วงค์ รัตนสิริ, วิทยา ถิฐาพันธ์

หน่วยมะเร็งอวัยวะสืบพันธุ์สตรี ภาควิชาสูตินรีเวชวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

ผู้ป่วยมะเร็งปากช่องคลอดระยะที่สี่สองรายที่ไม่สามารถทำผ่าตัดได้ในตอนแรก ได้รับสารเคมีบำบัด 2 ครั้ง แล้วพบว่าสามารถทำผ่าตัดได้ จึงได้ทำการผ่าตัดแบบ Radical vulvectomy with groin and pelvic nodes dissection ในผู้ป่วยรายแรกไม่พบมะเร็งในขอบแผลผ่าตัดและต่อมน้ำเหลือง ส่วนอีกรายพบมะเร็งที่ต่อมน้ำเหลืองทั้งสองข้างจึงได้รับรังสีรักษาต่อ จากการตรวจติดตามครั้งสุดท้ายผู้ป่วยทั้งสองรายยังมีชีวิตอยู่โดยปราศจากมะเร็ง

Two cases of FIGO stage IV, inoperable squamous cell carcinoma of the vulva were given primarily with two courses of chemotherapy. The tumor masses in both cases turned to be operable and radical vulvectomy with groin and pelvic nodes dissection was performed. The surgical margin and lymph nodes were free of tumor in the first case while the other one had bilateral lymph nodes involved by the tumor and so radiotherapy was given. Both patients were in good health and free of disease at the time of last follow-up.

INTRODUCTION

Carcinoma of the vulva accounted for 3-5% of gynecological malignancies in most series[1-2]. It was found to be 2.22% at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University[3-4]. The mean age of the patients was 52 years. The most common histological type was squamous cell carcinoma (91.35%). About 70% were in stage I and II, and 30% were in advanced stage (III and IV). In recent years there were some

patients referred to our hospital with inadequate treatment, complications, or recurrent diseases.

The accepted treatment for all stage of squamous cell carcinoma of the vulva at present time is radical vulvectomy and bilateral inquinal lymphadenectomy. The survival of vulvar cancer patient in general is related to the extent of the disease. The corrected 5-year survival rate for all stage is around 75%. For stage I and II disease, the 5-year survival rate approaches 90%[1]. The overall 5-year survival rate at Srinagarind Hospital was 80.49%[4], 92.86% for operable cases and no patient survived up to one year in those inoperable cases. In spite of surgery and/or radiotherapy, nearly all patients with advanced disease (stage III and IV) die of tumour. Some of the radiated patients die of the ulcerated and infeced lesions.

Surgery is, nevertheless, considered to be the most effective treatment. But in some locally advanced or inoperable tumors, it has been reluctant to perform the operation. More recently there has been a trend toward less redical surgical procedures in selected patients[5]. Nonsurgical approaches including radiotherapy and chemotherapy[6-7], and radiation alone[8-10] have been tried. Preoperative radiation to shrink the tumor and render it operable has been tried[11-13], as well as preoperative chemoradiotherapy in advanced vulvar cancer[4]. The results were still unsatisfactory in most series.

Neo-adjuvant chemotherapy for advanced squamous cell carcinoma of the cervix has been studied with satisfactory results[15-21]. Strzinar and coworkers[22] recommended preoperative chemotherapy to be more efficient and more convenient for treating the patients with advanced or recurrent carcinoma of the vulva in comparison with that of preoperative radiotherapy. Bortolozzi and coworkers also reported the regression of the tumour clinically and/or pathologically[23]. Using the combination of cisplatinum, vincristine and bleomycin as neoadjuvant chemotherapy in 5 cases, Itala obtained all objective response[24]. Using the Durrant regimen, the EORTC group obtained a 60% response in patients with inoperable vulvar cancer and surgery became possible in 7 of 20 patients[2]. To explor the role of neo-adjuvant chemotherapy in patients with advanced carcinoma of the vulva in order to diminish the tumour bulk to make radical surgery possible in those inoperable cases, the combination of Cisplatinum 50 mg/sq.m., Mitomycin-C 10 mg/sq.m. and 5-fluorouracil 500 mg/sq.m. has been adapted from Kalra et al[14].

CASES PRESENTATION

CASE I M.S. I.P. BN 8429

A 59-year-old, para 6-0-0-6 last 24 years, who experienced her last menstrual period at the age of 50 has had vulvar itching and a lump for approximately one year. She went to a district hospital and was then referred to a provincial hospital. Excision of the lump was done but without histological report informed and she was home. Two months prior to this admission, the lump was again enlarged and became so severe that she could not performed her normal household duties. She went to the same district hospital and was referred to Srinagarind Hospital on December 1, 1986. On physical examination, she had a small figure, thin, weak and cachectic with the weight of 29 kg., height of 121 cm., blood pressure of 100/70 mm.Hg, pulse rate 80/min., respiration 20/min. Examination of the head, eyes, ears, noses and throat were unremarkable. The breasts contained no masses, the nipples were everted and there was no discharge. The abdomen was flat, no organomegaly, no tenderness to deep palpation, and no CVA tenderness.

There was a large lesion at the right side of the vulva, 7 x 3 cm. cauliflower mass at the right labia majora, clitoris connected to the ulcerated lesion 7 x 3 cm. at the right labia minora (Figure Ia). The lesion fixed to the pubic bone anteriorly but did not involve the urethral meatus or the anal area. The lower third region of the right vaginal wall was also involved. The cervix was cleaned and the uterus was normal in size and mobile. The adnexae were not palpable. There were hard and fixed nodes with the size of 2 x 2 cm. on both inquinal regions.

Laboratory data revealed hemoglobin 9.8 mg%, haematocrit 31%, WBC 11,600 cells/sq.mm., N = 63%, E = 16%, L = 18%, M = 3%, platelets 200,000 cells/sq.mm., few target cells. Blood group O, BUN 22.6 mg%, creatinine 1.5 mg%, albumin 3 g%, globulin 5.3 g%, SGOT 15.5 Sigma units. Normal urinary examinations, normal EKG, negative chest x-ray, normal IVP. Stool examination revealed black colour and presence of opisthorchis ova.

According to FIGO staging, she was classified as stage IV.

On December 11, 1986, she was given the first course of combination chemotherapy, the second couse on January 8,1987. Radical vulvectomy with groin and pelvic nodes dissection was performed on February 18, 1987.

Response to chemotherapy

After the first course of chemotherapy, the lesion was gradually decrease in size about 50% and two weeks after the second couse, the lesion was decreased to about 20% of the original size (Figure Ib). The groin nodes were then not palpable. The tumour was mobile and no more fixed to the bone. The lesion was then considered to be operable.

Toxicity

According to the Gynecologic Oncology Group Adverse Effects Criteria (December 1980), she had grade 3 haematological toxicity, grade 2 nausea-vomitting, grade 3 stomatitis, grade 3 hair loss and grade 2 hematuria.

The gross lesion of the surgical specimen revealed abrasive lesion 5 x 3 cm. in size confined to the right labia majora and minora (Figure Ic). No lesion at the clitoris, vagina. No gross enlargement of groin and pelvic nodes. Histologically, the surgical margins were free, no tumour cell detected at any lymph nodes.

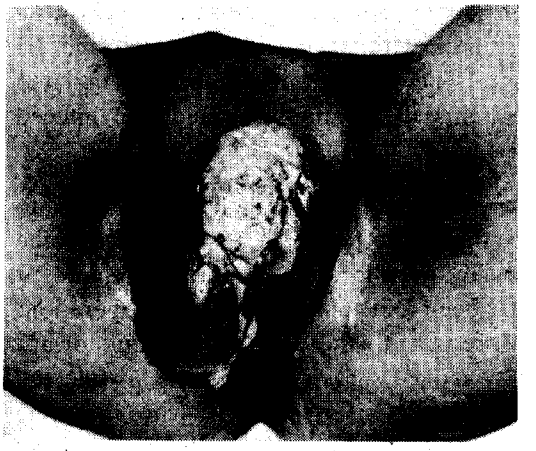
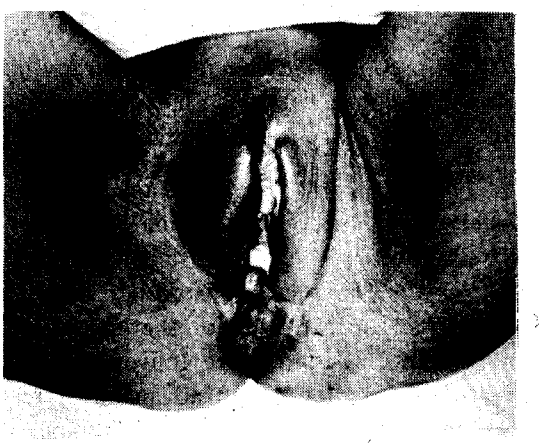


Figure Ia) before chemotherapy



Ib) before operation

Ic) specimen after radical vulvectomy

After 2 weeks of operation, there were small lymphocysts at both sides of the groins which were relieved by aspiration. The surgical wound was completely healed three weeks after operation and the patient was discharged and planned for follow-up every 3 months in the first year.

CASE II MS. N.N. BN5812

A Thai female, widow, 63 years old, para 7-0-0-7 last 21 years. Her last menstruation was at the age of 54. She came to the out-patient department of Srinagarind Hospital on November 27, 1986 with the chief complaint of bleeding per vagina for 8 months. Two years prior to this admission, she had a small ulcer with itching at the clitoris. The ulcer grew slowly until one month before, it was observed to be more enlarged and by the last 5 days profused bleeding occurred. She had no history of tuberculosis, diabetes hypertension, or any history of surgery. She had the experiences of two marriage and then divorced.

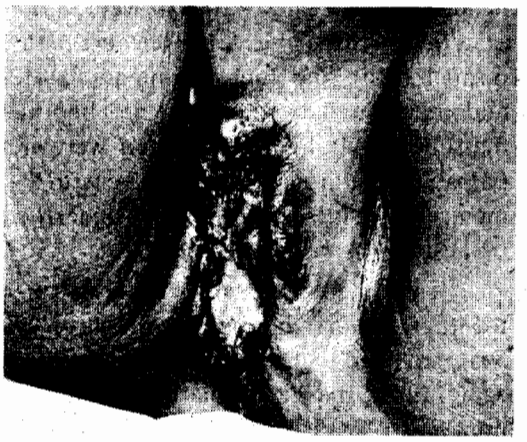
On physical examination she was an elderly, thin but looked healthy woman, weight of 36.5 kg., height 145 cm., blood pressure 90/60 mm Hg., pulse rate 98/min., respiration rate 20/min. Examination, of head, eyes, ears, noses, throat were in normal limit. No cervical lymphadenopathy, normal heart and lung examination. Her abdomen was flat, no ascites, no abnormal mass detected, liver and spleen were not palpable. The groin nodes were 3 cm. in diameter both sides, fixed to the underlying tissues.

There were three vulvar lesion blended together. At the clitoral area the ulcer was 5 x 4 cm. fixed to the underlying pelvic bone. The ulcer at the right labia majora and minora was 4 x 3 cm. in diameter, also fixed and the perineal ulcer was 10 x 3 cm. mobile (Figure IIa).

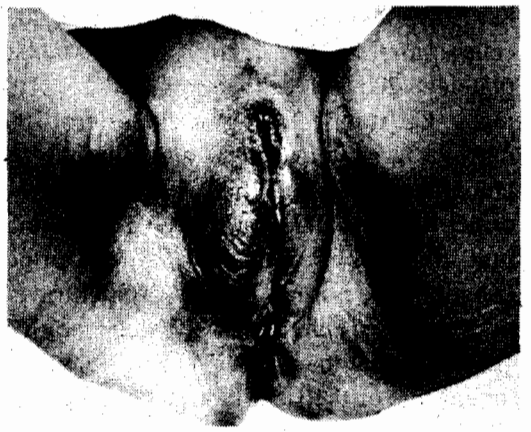
Laboratory data showed; haemoblobin 8.4 gm%, haematocrit 27%, WBC 9,200 cells/sq.mm, N 71%, L 20%, E 6%, M 3%, platelets 200,000 cells/sq.mm, BUN 11.9 mg%, Creatinine 2.1 mg%, cholesterol 100 mg%, total protein 6.5 g%, albumin 3.4 g%, globulin 3 g%, total bilirubin 0.33 mg%, direct bilirubin 0.08 mg%, SGPT 12 Sigma unit, SGOT 21.5 Sigmaunit. Normal urine examination, normal chest x-rays. Intravenous pyelography showed degenerative changes of lumbar spines and chronic pyelonephritis of the right kidney. examination showed hook worm and opisthorchis volvae.

Punch biopsy was done on the vulvar ulcers and the histological report revealed squamous cell carcinoma, large cell, non-keratinizing type. The FIGO staging was considered as stage IV.

She was given 2 courses of neo-adjuvant chemotherpy in half dose due to rather poor renal functions. Cisplatinum 30 mg. intravenously at day 1, Mitomycin-C 10 mg. intravenously at day 1 and 5-fluorouracil 200 gm, intravenously at day 1-5. The first course of chemotherapy started on December 11, 1986, the second course on January 6, 1987. After evaluation of chemotherapy as partial response she was performed radical vulvectomy with groin and pelvic nodes dissection on February 13,1987.



IIa) before chemotherapy



IIb) before operation

IIc) specimen after radical vulvectomy

Response to chemotherapy.

Three weeks after the first course of chemotherapy, there was no bleeding observed, the lesion at the clitoris, labia and perineum decreased in sizes to 3 x 3 cm., 0.5 x 0.5 cm. and 5 x 2 cm. respectively. Three weeks after the second course, the lesion was 2 x 2 cm, no lesion and 5 x 2 cm. respectively (Figure IIb). Both inguinal lymph nodes were still 1 cm. in diamerter but not fixed to the underlying tissues. During the couses of chemotherapy she had nausea and vomitting grade 2 relieved by antiemetics. She also had myelosuppression grade 1 but no alopecia.

Surgical specimen revealed enlargment of both inguinal nodes, the whole tumor removed was 4.5 x 4 cm. (Figure IIc). The histological examination of the surgical margin at the perineum was not free of tumour. Both inguinal nodes were invaded by the tumor. So irradiation was given externally. She was considered to be free of disease at the last follow up visit.

DISCUSSION.

The problem of treatment of vulvar cancer patients at Srinagarind Hospital in the last few years was that the patients come with late and advanced stage diseases of which the result was not satisfied. Inspite of radiotherapy given, no single case survived up to one year[4] This was primarily due to the inoperability of the disease. Preoperative radiotherapy had been tried in some case but unevenful ulceration as well as infection resulted in dangerous surgery. Recently, neoadjuvant chemotherapy has been reported to be useful in advanced cervical cancer[15-21] Mangioni et al[2] reported the result of treating 26 vulvar cancer patients by using Durrant's regimen; Bleomycin, CCNU, and Methotrexate with 3 complete response and 3 partial response 14. Kalra et al combined Mytomycin-C and 5-fluo-

rouracil preoperatively and obtained a good result. The Cisplatinum and 5-fluorouracil combination was also used as an induction chemotherapy [25]

The combination of the three drugs as preoperative neoadjuvant chemotherapy in this study gave a promising result. Decreasing in tumour size and nodal metastasis enabled the surgery possible in both cases. The full-dose administration as in case 1 gave a better response than the half-dose used in the second, but the toxicity was more severe and needed closer observation. The number of courses to be given is one of topic to be titrated. Most neoadjuvant chemotherapy protocol in cervical cancer was 3 courses administration but for economical reason, less course was considered in this institute.

From this pilot study it could be concluded that;[1] Neoadjuvant chemotherapy by using the combination of Cisplatinum, Mitomycin-C and 5-fluorouracil is effective for advanced, inoperable vulvar cancer, and made the disease operable. 2) In the recommended dose, two courses are enough for preoperative use. 3) Toxicity may be severe and close observation is mandatory in these old patients. 4) Conservative surgery should be considered for those young patients who still has sexual activities.

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