Topical treatment of vaginal recurrence of endometrial carcinoma with 5-fluorouracil: case-report

N. Surico, R. Ribaldone

Department of Medical Sciences, University of Turin, 2nd Faculty of Medicine and Surgery, Institute of Gynaecology and Obstetrics, Novara (Italy)

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Introduction

During recent years an increase in the incidence of endometrial carcinoma has been observed in western countries [1]. About a third of the women with this neoplasia have a recurrence after the operation and the following radiotherapy.

It emerges from the literature that more than 20% of the women at first clinical stage present an extra-uterine diffusion of the pathology and then a high risk of recurrence [2, 3, 4, 5].

Case-Report

A case of an 80-year-old woman, P0000, in physiological menopause since the age of 52 is presented.

In June, 1994 she underwent a total laparohysterectomy with bilateral salpingo-oophorectomy because of recurrent metrorrhagias and a fibrous uterus.

After surgery, the woman received radiotherapy with a linear accelerator (photons 18 MV) at 45 Gray for five weeks.

The woman had already undergone a diagnostic and therapeutic curettage with a negative report on 31 May, 1994. The histological report showed a poorly-differentiated endometrial adenocarcinoma with aspects of muciparous and squamous metaplasia deeply penetrating the uterine wall (stadium pT1c).

In December, 1995 she presented with some blood loss and was admitted to the Obstetrics and Gynaecological Clinic of Novara.

Clinical examination showed a bleeding one centimetre tumefaction on the third medium of the left vaginal wall. All instrumental examinations (lower and upper abdominal ultrasonography, CT, scintigraphy) to evaluate the extention of the neoplasia which proved negative.

The woman began treatment with megestrol acetate (two tablets a day) and underwent asportation of the lesion.

The histological report showed a nodose infiltration of the vaginal wall by a poorly-differentiated adenocarcinoma with unharmed borders of the lesion.

Five percent of 5-Fluorouracil (5FU) cream was applied to the third medium of the left vaginal wall as follows: one application a week (first week of treatment), two applications every two days (second week of treatment), one application a day for five days (third week of treatment) (Table 1).

Table 1. — *Indications for topical treatment with 5-fluorouracil*

Bowenoid Papulosis	von Krogh (1976)
HPV lesions of the urinary meatus	von Krogh (1976)
Vaginal condylomas	Férenczy (1984)
Prophylaxis after surgery of vulvo-vaginal condylomas	Krebs (1986)
Vulvar condylomas	Pride (1990)
Condylomas of anus and perineum	De Palo (1992)
VAIN	Sanchez Gonzalez (1993)

On 22 April, 1996 multiple biopsies were executed on the outpatient's vaginal walls; they were all negative.

Discussion

Considering that the progression of endometrial carcinoma depends on the estrogens and progesterone, the proven anti-estrogenic effects of progestogen are very effective in the treatment of well-differentiated adenocarcinoma (G1) [6].

At the beginning of the 60's Kelley and Baker proved the therapeutic efficacy of progestogen against endometrial carcinoma [7].

In fact, progestogen at a high dosage has a good response against advanced endometrial carcinoma. It acts anti-estrogenically because it reduces the concentration of estrogen receptors and activates estradiol 17ß-hydroxysteroid dehydrogenase which converts a strong estrogen, estradiol, to a weak one, estrone. Progestogen also activates estrogen-sulfonyl-transferase which sulfates the estrone released by the cell.

Progestogen also acts on the hypophysis inhibiting the LH, the FSH and the target cells stopping the nucleic acids and reducing the mitotic index [8, 9, 10]. The most widely used progestogens are medroxyprogesterone acetate and megestrol acetate.

We must not forget the importance of chemotherapy (mono or polychemotherapy), which must be reserved for women who do not respond to hormonal therapy or who present a wide diffusion of the neoplasia during diagnosis.

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The most widely used monochemotherapies are adriamycin, cyclophosphamyde, 5-fluorouracil, and cisplatin, and their association seems to produce a greater therapeutic efficacy (polychemotherapy). However, we must remember that the data on the polychemotherapy used to treat endometrial carcinoma are discordant.

In fact, Yamamoto and Okada assert, in their review published in 1992 [6], the superiority of polychemotherapy in comparison to monochemotherapy, but at present there are no data that definitely show a greater efficacy of polychemotherapy if compared to monochemotherapy with adriamycin [11, 12, 13].

Supposing that the development of endometrial cancer depends on estrogens, in 1979 Swenerton *et al.* [14] described tumor regression in four of the seven women treated with tamoxiphene for advanced endometrial cancer. Tamoxiphene is a molecule derived from triphenylethylene which has an antineoplastic action inhibiting the bond between estrogen and its receptors [15].

In our case, seeing the impossibility of beginning chemotherapy because of the patients poor cardiac-circulatory condition, we decided to review the international literature to try to find an adequate topical treatment for her. Topical treatment with 5-fluorouracil is not reported in the protocols of oncological therapy, but has had excellent results in the therapy of viral and precancer of the female and male genital tract. Gonzalez Sanchez [16], in a review in 1993, shows the adequacy of therapy with 5-fluorouracil in eight women treated for intraepithelial neoplasia of the vagina, by doing a comparative study of cryotherapy, cryotherapy-5-fluorouracil and radiotherapy.

Geo von Krogh treated areas of boweniod papulosis, lesions of the urinary meatus [17]; disappearance of the lesions has been verified in 90 per cent of the cases.

Its application in vaginal condylomata is reported by Ferenczy [18] (cure rate of 3.5%).

Pride [19] obtained a cure rate of 68 per cent in vulvar condylomata.

Krebs [20] performed a prophylactic treatment with 5-FU after surgery of vulvovaginal warts for condylomata, showing a significant reduction of recurrence versus non-treated cases (13% versus 38%).

Its use is also indicated by DePalo in the treatment of subclinical infections of the anus and perineum [21] (Table 2).

In our case, a topical treatment with 5-FU cream (5% to the megestrol acetate assumption) was used. Due to the patient's poor condition, she was not able to undergo monochemotherapy. Antimetabolite, which interacts with the synthesis of the nucleic acids, was used because the recurrence involved the third medium of the left vaginal wall, a structure particularly sensitive to 5-FU.

We did not limit ourselves to simple therapy with progestogen because histologically the lesion was a poorly-differentiated adenocarcinoma (G3), scarcely responsive to the progestogens due to a poor concentration of receptors [22].

Nonetheless, we think that progestogen therapy is fundamental despite the type of the carcinoma. In fact, it induces improvement because progestogen has a psycotonic effect and stimulates protein anabolism.

For precautionary reasons a treatment with interval-spaced administrations was adopted, with a single dose of 2.5 grams, as mild local toxicity may lead to complications such as dysuria, pain, burning, erythema and ulcerations. A cream of zinc oxide was used to protect the vulvar mucous and to avoid vulvitis with ulcerations.

In 1991, Goodman *et al.* [23] pointed out the development of vaginal adenosis and clear cell carcinoma eight months after 5-FU treatment for urogenital condylomas in women not exposed to DES, even though this supposition is very debatable.

Up to now, the patient who has been treated by our oncological clinic is asymptomatic and clinically and histologically negative (multiple biopsies have been done).

In conclusion, we can assert that the first choice treatment for advanced endometrial carcinoma (recurring after surgery) is based on the use of progestinic therapy at a high dosage, and polychemotherapy. The choice of treatment should be made considering the patient's general condition and the biological characteristics of the endometrial cancer.

We believe topical treatment with 5-FU to be a good therapeutic approach when the woman's general condition is poor, especially in regard to her cardiocirculatory status which is fundamental in choosing mono or polychemotherapy.

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Address reprint requests to:
RAFFAELLA RIBALDONE
Via Guido Gozzano, 1
13048 Santhià (VC), Italy