Low-dose 5-fluorouracil adjuvant in laser therapy for HPV lesions in immunosuppressed patients and cases of difficult control

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Summary

The authors established a protocol for the use of 5-fluorouracil (5FU) adjuvant in lasertherapy for clinical and subclinical HPV infection in immunosuppressed patients, persistent lesions and as reinforcement treatment in cases of poor progress. Sixty-four patients were evaluated, of whom 26 were immunosuppressed, 34 presented persistent lesions and four received intravaginal reinforcement treatment with 2.5 g 5% 5FU every two weeks, or biweekly vulvar reinforcement after lasertherapy. On average, five 5FU courses were used, but in the immunossuppressed patients its use was maintained indefinitely. The rate of complete response was 66%, but the immunossuppressed patients showed less response (46.2%) when compared with the persistent lesion/reinforcement treatment group (78.9%). The responses were positive in the two groups when compared to that with no response. We deem the use of low-dose 5FU an excellent alternative in cases of difficult HPV progress, presenting a low cost and minimal side-effects.

Key words: 5-fluorouracil; HPV.

Introduction

Human papillomavirus produces an infection where the affected area represents a focal break in the local immunity control [1].

Reduced systemic cellular immunity is an important risk factor for human papillomavirus infection and a cofactor in the genesis of HPV-associated neoplasms. The degree of cellular immunodeficiency determines the course of the lesion. In women with renal transplant the prevalence of HPV in the uterine cervix ranges from 20 to 45%, the development of cervical intraepithelial neoplaisa being five times, and invasive cancer, 17 times greater, when compared with the control group [2].

In women with immunodeficiency syndrome, prevalence of cervical HPV is of the order of 38 to 75%. These women are also at a higher risk of developing intraepithelial and invasive neoplasms. CINs are more severe, the lesions are more extensive, affecting more than one site, with persistence and recurrence after treatment [3].

The so-called preneoplastic syndrome of the inferior genital tract is that where HPV infection, associated with intraepithelial neoplasia, affects the cervix and/or the vagina and/or the vulva.

Failure in the treatment of these lesions is often related to detection of HPV in the adjacent epithelium which is normal on colposcopy.

These situations are difficult to control using the known forms of treatment, such as destruction by trichloroacetic acid or CO_2 laser vaporization.

The literature mentions that chemosurgery using 5-fluorouracil (5FU) associated with laser evaporation, laser excision and high frequency surgery improves remission rates, with lower indices of relapse. Sillman *et al.* [4] have indicated 5FU for patients with HPV and immunosuppression, preneoplastic syndrome of the inferior genital tract, vaginal intraepithelial neoplasia, patients at high risk for relapse and persistent disease.

Ferenczy [5], using 5FU adjuvant in laser vaporization for intravaginal condylomata, observed that relapses were less frequent when comparing with cases where only laser vaporization was applied.

Krebs [6] indicates its use for patients with immunosuppression during an undetermined period; in difficult but immunocompetent cases, its monthly use for a period of six months.

Maiman *et al.* [7], using 5FU adjuvant in laser vaporization or excision of the transformation zone in HIV-HPV positive women with high-grade CIN, observed that relapses occurred at a lower percentage when compared with those who did not use it.

Based on these studies, and due to the constant relapses, specially in the immunosuppressed women, we developed a protocol for the use of 5FU adjuvant in the treatment with CO_2 laser.

Thus we intend to show the response to the association of 5FU with CO_2 laser vaporization and/or excision in patients with isolated or multifocal and/or multicentric HPV lesions, either immunosuppresed or presenting residual lesion detected early after CO_2 laser.

Materials and Methods

In this protocol 64 patients with a mean age of 34.8 years (17-75) were included, of whom 26 were immunosuppressed, 34

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presented persistent lesions after treatment with laser and four cases needed reinforcement treatment after treatment of cancer of the uterine cervix, because these patients are at a high risk for relapse. Of the immunosuppressed patients, 12 had a renal transplant, one a liver transplant, 12 were receiving therapy with corticoids and one was an oncologic patient.

Thirty-four patients presented preneoplastic syndrome of the inferior genital tract, affecting two or more sites, with 28 characterized as low-grade, and six as high-grade. In 30 the syndrome affected only one site of the inferior genital tract, with 15 being low-grade and 15 high-grade.

The initial treatment in 59 patients was CO_2 laser vaporization and/or excision of the clinical and/or subclinical lesions, with power ranging from 10 to 25 W and continuous emission mode. In the cases of voluminous papillomatous lesions, excision was performed with laser with focalized light beam. Two weeks after the procedure, the 2.5 g intravaginal 5FU scheme every two weeks was started, always followed by a 3-day application of clostebol acetate. When a vulvar lesion was present, we recommended a twice a week application of a fine layer of 5FU to the diseased area followed by washing after two hours.

In five patients the use of intravaginal 2.5 g 5% 5FU every two weeks and/or vulvar, biweekly, on the lesion was chosen, totaling three to five weeks of treatment. This condition was indicated for patients with voluminous multifocal and multicentric lesions, with the purpose of reducing the lesion in order to minimize the area to be destroyed by laser. Thereafter laser vaporization was performed and within two weeks the 5FU scheme was started again as described.

In the patients who did not present immunosuppression, when no residual lesion was observed on control after three weeks, the 5FU scheme was immediately started (called persistent group).

The patients were reevaluated after each 3-4 doses in order to follow the progress of the clinical picture and to survey any side-effects. After disappearance of the clinical and/or subclinical lesion, 5FU was used once a month; for immunosuppressed patients, 5FU was maintained continuously during the month. In the cases of persistence, three to ten applications every two weeks were completed according to the disappearance of the lesions. In the cases of reinforcement treatment, ten cycles were used. If emergence of vaginal and/or vulvar lesions occurred, the treatment was discontinued until the area was epithelialized, aided by clostebol acetate.

If there was persistence or appearance of new lesions, laser was reapplied.

After clinical control of the lesion, cytocolposcopy was performed every three months during the first year and every six months from the second year on.

Complete clinical response was defined as normal cytology and colposcopy; partial response, when there was a decrease of more than 50% of the initial lesion area or when low-grade cytologic alteration was maintained without colposcopic lesion; stable disease, when there was less than 50% reduction of the lesion; and progressive disease, when there was more than 25% growth of the lesions.

Results

Sixty-three women completed on average five 5FU courses. The scheme was discontinued in one of the patients because of side-effects.

A complete response was obtained in 42 cases (66%); in 14 cases (22%) a partial response, of which three cases with only cytological alterations showing low-grade lesion, two cases with keratinized vulvar lesions and five with extensive multifocal disease. Seven cases (11%) presented stable disease and one case (1%) progressive disease due to the irregular use of the drug in a patient with serious immunosuppression and intense side-effects.

Mean time for the observation of clinical improvement was 4.3 months. On average the follow-up time of the patients was 18 months.

Side-effects such as chemical vulvovaginitis, accompanied by ulcers in the vagina and vulva were observed in 22% of the cases. These effects tended to be minimized by the use of clostebol acetate. We had to discontinue the chemical treatment in only one case because the patient could not stand the adverse symptomatology.

In eight cases a molecular biological assay by hybrid capture for HPV was performed before starting the treatment, whose result showed a high viral load of the virus in the oncogenic group. In the control group, after the end of the treatment, seven patients reached a negative viral load, and one patient attained a low viral load, with all of them showing complete remission of the lesion. Table 1 shows the types of response (CR - complete response, PR - partial response, SD/PD - stable disease/progressive disease) according to the immunosuppression group and the persistent disease and reinforcement treatment group.

Table 1. — *Types of response according to the immunosuppression group and the persistent disease and reinforcement treatment group.*

Group Response	Immunosuppression	Persistent/ reinforcement treatment	Total
CR count	12	30	42
% within Group	46.2%	78.9%	65.6%
PR count	9	5	14
% within Group	34.6%	13.2%	21.9%
DE/DP count	5	3	8
% within Group	19.2%	7.9%	12.5%
Total count	26	38	64
% within Group	100%	100%	100%

p = 0.026*; CR = ; PR = persistent reinforcement. DE/DP.

Discussion

Most HPV-induced lesions can be treated in a physician's office. CO_2 laser is a safe method, with the removal of any volume of diseased tissue and quick epithelialization and no scarring. The method, however, cannot hinder reactivation of latent infection of the adjacent or deep areas of the skin appendices, specially in cases with a difficult course and in the immunosuppressed. An adjuvant method could help in the management of these cases.

The use of high-dose regimens of topical 5FU showed to be inefficient, presenting many side-effects. However in non-cytotoxic doses it prevents viral relapse. 5-fluorouracil, when used individually, is unable, in some cases, to necrotize the vaginal or cervical epithelium up to its basement membrane [8].

5-fluorouracil is a potent cytotoxic agent which inhibits cellular DNA and RNA synthesis. It is a DNA antimetabolite that promotes the chemical necrosis of the lesion. It has an antiproliferative effect, an immunostimulating effect with local release of endogenous interferon and an antiviral effect inhibiting HPV replication. Krebs [6] describes healing rates of approximately 85 to 90% in HPV-induced lesions. It penetrates better mucous membranes and diseased tissue than normal skin.

The results of previous studies on the association of both laser and 5-fluorouracil methods encouraged us to carry out this protocol.

In this study we observed significant differences between the types of response of the two groups, with a higher rate of positive results as compared with unsatisfactory results. The complete response rate in the immunosuppression group was 46.2% in contrast to 78.9% for the cases with persistent lesions and reinforcement treatment. Comparison between the groups showed a higher rate of complete response in the persistent lesions and reinforcement treatment group. These patients, in spite of the difficulty of the response, possess a healthy immune system which, being stimulated by adjuvant therapy, reacts against infection due to HPV.

The partial response rate for the immunosuppresion group was 34.5% and 13.2% for the persistent and reinforce treatment group. It can be observed that in the immunosuppression group the lesions tend to have a partial response, maintaining some type of residual disease due to the pathologic inability of the immune system to react against this affection.

Stable or progressive disease rate was low in the persistent lesion and reinforcement treatment group (7.9%). Contrariwise in the immunosuppression group, it was 19.2%, being higher than in the other group, but significantly lower than the positive response rates, showing that chemosurgery promotes therapeutic benefits, even with an enfeebled immune system.

On analyzing all 64 cases, we observed that the percentage of positive responses (CR+PR) was high (87.5%) when compared with that of the poor response (SD+PD) of 12.5%, demonstrating that chemosurgery has a significant therapeutic value in cases of difficult control of HPV infection. Immunosuppressed patients, with a tendency to multifocal and multicentric disease, persistent lesions after conventional treatment, specially intraepithelial neoplasias of the vagina, and cases known to have a poor prognosis, as those after oncologic treatment, are selected cases in which the use of 5FU is of great value, with more benefits than the side-effects that may occur.

Vaginal intraepithelial neoplasias (VAIN) seem to affect women with some degree of local immune weakness, because they reach the stable stratified epithelium which does not contain glands. The treatment of these lesions with 5FU alone at a regimen of 1.5 g for ten weeks showed 77% remission according to González Sanchez *et al.* [9]. In our group of patients, on analyzing the cases of persistent VAIN, without associated pathologic immunosuppression, we observed after CO_2 laser vaporization complete response in 22 (81.5%)of the 27 studied cases, encouraging us to use promptly 5FU adjuvant on any sign of lesion maintenance. These results are similar to those of other authors [4, 5, 8, 9].

Side-effects such as vulvovaginitis were minimal, specially because of the used low dose and the association with clostebol acetate. However, based on the study by Syed *et al.* [10], the patients who presented sensitivity to the 5% concentration benefited from the use of cream prepared at 1% in hydrophilic gel.

This study does no attempt to prove that HPV infection is effectively treated with 5FU. Further studies are required to prove its effectiveness with a longer follow-up period.

Conclusions

The established protocol for the use of 5-fluorouracil adjuvant in lasertherapy for patients with clinical and subclinical HPV infection, with immunosuppression or persistent disease after treatment presents the following conclusions: it is a good option in cases of difficult control, has few side-effects, is of low cost and of easy application with a drug of triple – antiviral, antiproliferative and immunostimulating – effects.

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