EJGO European Journal of Gynaecological Oncology

Imiquimod cream and CO2 laser vaporization in vulvar intraepithelial neoplasia (VIN) 2/3 treatment

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Summary

Objectives: To compare the use of topical 5% imiquimod (IMQ) cream or CO2 laser vaporization as the treatment of vulvar intraepithelial lesions (VIN) 2/3 and to evaluate the degrees of residual or recurrent lesions. *Materials and Methods:* Twenty-nine women with VIN 2/3 were separated into two groups, according to the proposed treatments. All were submitted to collection of vulvar swabs for DNA genotyping of human papillomavirus (HPV), vulvoscopy, and biopsy of the found lesions. After treatment they were followed up in quarterly consultations to (until) possible appearance of new lesions or along one year. *Results:* The findings were similar in effectiveness and presence of residual or recurrent lesions on the performed treatments. However, patients treated with topical 5% IMQ cream had less severe lesions in histological recurrence when compared to those submitted to the CO2 laser vaporization. *Conclusions:* The effectiveness of topical 5% IMQ cream was similar to that of CO2 laser vaporization. There was no difference between the treatments for the presence of residual or recurrent lesions. However, patients who received IMQ had less aggressive lesions than those submitted to the treatment with CO2 laser vaporization.

Key words: Vulvar intraepithelial neoplasia; CO2 vaporization; Imiquimod cream.

Introduction

Vulvar intraepithelial neoplasia (VIN) showed an increase in incidence over the past 40 years in young women, with the average age dropping from 50 to 39 years. About half of women with VIN has other associated neoplasias in the lower genital tract, usually in the cervix [1, 2]. The evolution of some cases from VIN to epidermoid carcinoma of the vulva is related to usual and differentiated VIN, so that the age distribution of VIN is biphasic [3, 4]. Although considered a premalignant condition, the spontaneous regression of VIN has been described in young patients, under 35 years, immunocompetent, and with small lesions [5, 7]. The choice of appropriate therapeutics must be preceded by reliable anatomopathological diagnosis, seeking individualization of factors related to the patient, the lesion, and also with the technique to be applied [8-9].

The use of CO2 laser was introduced and established in the treatment of vulvar lesions induced by human papillomavirus (HPV) due to discrete thermal effects in the tissue, with good aesthetic and functional results. CO2 laser vaporization destroys the tissue to be treated, preventing the histological analysis, and requires the exclusion of invasive disease [10-11]. Topical 5% imiquimod (IMQ), a compound of the imidazoquinolones family, is considered a modifier for the tissue immune response and pro-inflammatory agonistic agent of transmembranic proteins toll-like receptor (TLR) 7 and 8. IMQ induces remotely regression of other HPV synchronic lesions and reduces the viral load by more than 90% of cases, assisting in the formation of immunological memory, which is important for fighting the recurrences [12-14].

Materials and Methods

The authors selected 29 women with VIN grade 2 (VIN 2) and grade 3 (VIN 3) related to HPV treated at the outpatient clinic of Lower Genital Tract Pathology sector of the Gynecologic Disease Prevention Center (NUPREV), from the discipline of General Gynecology, Gynecology Department of the Escola Paulista de Medicina – Universidade Federal de São Paulo (EPM - UNIFESP) during the period from 2006 to 2009. Non-inclusion criteria considered were the following: the histopathological diagnosis of VIN differentiated type, the personal history of vulvar dermatosis and / or lower genital tract carcinoma; pregnant women; women suffering from acquired immunodeficiency syndrome; severe immunodeficiency of any etiology; suspected cytocolpusvulvohistopathological of the neoplastic invasion in any follow-up of the lower genital tract, and still current treatment of HPV-induced vulvar lesion with any therapeutic modality.

All women were objectively informed about the nature of the study and signed the post-informed consent form for voluntary participation. The Project was approved by the Research Ethics Committee of EPM-UNIFESP. The study consisted of two phases: the first stage with the selection and treatment of patients and the subsequent second follow-up stage. In the selection phase, all patients

Revised manuscript accepted for publication January 26, 2016

submitted to an anamnesic questionnaire, the collection of cervicovaginal cytological smear and vulvar lesions smear to DNA detection and genotyping of HPV. The data obtained at the first consultation were: ethnicity, age, parity, number of sexual partners, smoking habits, mean duration of lesion in months since its appearance until the beginning of treatment, previous treatments, associated diseases, and use of medicaments. Colposcopy and vulvoscopy were performed for implementing the directed biopsy of the identified lesions.

After an electronic draw, two groups were defined for the application of each of the proposed treatments: 1) CO2 laser vaporization guided by colposcopic vision, with the aim of defining the edges, and the extent of the lesion, and the vaporization depth. The CO2 laser equipment was used coupled to a colposcope. With the help of a micromanipulator, directing of the spotlight to the lesion was made with the power of 20-W, three-mm safety margin, with defocused beam, with an average diameter of two mm. In non-hairy areas the vaporization was programmed to reach one-mm depth and three mm in hairy areas reaching the reticular dermis. 2) Topical 5% IMQ: the contents of a sachet with 250 mg of cream was applied on the affected area before sleeping. It was also indicated to wash the area at wake-up, after six to ten hours of application of cream. The procedure was repeated three times per week, during a minimum period of four through 16 weeks, varying according to the time of the lesions' disappearance. A complete response was defined as a complete disappearance of lesions; partial response when the lesions decreased more than 50% of extension; a stable or persistent disease when the lesions decreased less than 50% without further new lesions, and progressive disease when there was an increase in the number or size of lesions by more than 25%.

At the beginning of the therapy, new control consultations were carried out, being the first of them 15 days after the start of treatment and the subsequent consultations were monthly for review and evaluation of adverse effects. In the follow-up phase, the evaluations were started three months after the conclusion of the clinical conduct quarterly and held until the appearance of new vulvar lesions, or until complete one year of procedure.

The lesions found at follow-up were divided into persistent and recurrent. It was considered persistent lesion when three months after the end of treatment, it was still visible through vulvoscopy and recurrent lesion when, after the absence of lesion through vulvoscopy, there was a reappearance in a period longer than three months. In the presence of persistent or recurrent lesions, the emotional discomfort expressed by patients was considered and an option was given, by convention, to complete the treatment of all lesions with CO2 laser vaporization. In case that no lesion was found, the patients were recalled by phone or mail and in the absence of return, they were excluded from the follow-up stage.

The statistical analysis was performed using the Fisher Exact test for comparison between frequencies and proportions; likelihood ratio test for comparisons of two categorical variables with more than two categories in at least one of them. In all performed and applicable tests, the level of rejection of the null hypothesis equal to or less than 5% (0.05) was considered with statistically significant and marked with an asterisk (*). The analyses were performed using the statistical Statistical Package for Social Sciences (SPSS, v16.0).

Results

Among the 29 women with VIN 2/3, 14 were subjected to treatment with CO2 laser vaporization and 15 to treatment with topical 5% IMQ. There was no statistical difference between quantitative variables: age, ethnicity, menarche, first sexual intercourse, number of births, and number of partners. Similarly, there was no significance among categorical variables: smoking habit, use of contraceptive methods, presence of complaints, lesions characteristics, detection of viral DNA by PCR-HPV, and histopathological variant of vulvar lesions between the two treatment groups.

Similar clinical responses were observed (p = 0.43) in both treatments after 16 weeks of completion (Table 1). Two patients did not attend to the follow-up phase. In the remaining phase, in both clinical procedures, there were found similar results regarding the occurrence of residual or recurrent lesions (Table 2). One patient in the laser vaporization subgroup that presented recurrence did not authorize the performance of a new biopsy. A difference in histological grade of recurrent lesions biopsied during the follow-up among women subjected to the use of topical

Table 1. — *Distribution of 29 women, according to the therapeutic conduct and the clinical responses achieved.*

Clinical response	Imiquimod		Laser		Total	
	n	%	n	%	n	%
CR	12	80.00	9	64.29	21	72.41
PR	3	20.00	5	35.71	8	27.59
SD	0	0.00	0	0.00	0	0.00
PD	0	0.00	0	0.00	0	0.00
Total	15	100.00	14	100.00	29	100.00

Fisher Exact test p = 0.43.
Legend: n = number of patients; p = level of significance; % = percentage; CR = complete response; PR = partial response; SD = stable disease / persistence of disease; PD = progressive disease.

Table 2. — *Distribution of 27 women, according to the follow-up of three months after the completion of the conducts adopted.*

Vulvar lesion	Imiquimod		Laser		Total	
	n	%	n	%	n	%
Absent	6	42.86	6	46.15	12	44.44
Residual	2	14.29	3	23.08	5	18.51
Recurrence	6	42.86	4	30.77	10	37.05
Total	14	100.00	13	100.00	27	100.00

Fisher Exact test (p = 0.79).
Legend: n = number of patients; p = level of significance; % = percentage.

Table 3. — *Distribution of nine women, according to the severity of recurrent lesion.*

Vulvar Lesion	Imiquimod		Laser		Total	
	n	%	n	%	n	%
VIN 1 or CdAd	5	83.33	0	0.00	5	55.55
VIN 2/3	1	16.67	3	100.00	4	44.45
Total	6	100.00	3	100.00	9	100.00

Fisher Exact test p = 0.048(*).
Legend: n = number of patients; p = level of significance; % = percentage; VIN = vulvar intraepithelial neoplasia; CdAd = condyloma acuminata.

5% IMQ and CO2 laser vaporization, was observed with statistical significance ($p = 0.048$). The remaining women undergoing the treatment with the CO2 laser with recurrence showed high histological grade alterations, while 83.3% of patients treated with topical 5% IMQ showed lower histological severity of lesions compared to the initial VIN, i.e., low-grade neoplasia (Table 3).

Discussion

It is known that the frequency of VIN is low when confronted with cervical intraepithelial neoplasias, complicating the analysis of natural history, but the incidence of VIN 3 increased 411% from 1973 to 2000 in women younger than 65 years, mainly in the age range of 40-49 years. For many years, the preferential treatment of VIN was a surgical one, causing deformities, mutilations, functional changes in the vulva, and with significant recurrence rates. With the increase in VIN prevalence in younger women, studies with less aggressive therapeutical options have been performed, attempting to achieve procedures with effective clinical response and better prognosis [15-19].

Several publications about the use of topical 5% IMQ in VIN 2/3 demonstrate a clinical importance of medication with good therapeutic response, lower incidence of recurrences, reduction in the size of vulvar lesions, and converting the vulvectomy in simple local excision of the lesions, when no complete response to the treatment occurs [20-25].

All patients submitted to treatment with IMQ and CO2 laser vaporization showed a partial or complete response, without statistically significant difference between treatments ($p = 0.43$). It is thus demonstrated that both therapeutic resources are considerable alternatives for the treatment of VIN 2/3. In addition, the objective of the treatment of VIN 2/3 aims to improve the clinical symptoms, prevent the invasion without great damages in function and vulvar anatomy, especially in young women. The findings are in agreement with Bruchim *et al.* who evaluated 50 women with VIN 2/3, submitted to different treatments [26]. Similar findings regarding good response to treatment with the CO2 laser vaporization were also observed by Sideri *et al.* and Ribeiro *et al.* [27, 28].

It is interesting to note that at follow-up of women with vulvar lesion type VIN 2/3, a number of similar cases of residual lesion or recurrence between the two groups was diagnosed. However, among women with recurrence who used topical 5% IMQ, it was found that most of them had less severe histological lesions, diagnosed with VIN 1 or condyloma acuminata. In patients treated with laser vaporization of CO2 with local recurrence, all of them maintained the initial histological grade, i.e., VIN 2/3. However, Gentile *et al.*, following-up women with VIN treated with surgical excision or surgical excision associated with IMQ 5%, did not observe significant difference between the histological severity of recurrent vulvar lesions and the use of IMQ [29].

The present findings differ from those described by Wallbilich *et al.*, in which the recurrence after treatment of VIN 2/3 was more frequent, with statistical significance in cases submitted to CO2 laser vaporization compared with the excision or use of topical 5% IMQ [30]. This fact possibly occurred due to the inclusion of patients with immunologic deficiencies, because it was a retrospective study and lack of information on the technical skill of the executer of the CO2 laser vaporization [30]. No progression to invasive vulvar neoplasia was diagnosed during the follow-up.

Conclusion

The present authors may conclude that the response to treatment of patients with VIN 2/3 with topical 5% IMQ was similar to CO2 laser vaporization. However, with these results, it was evident that the treatment with this medicine plays an relevant role in decreasing the recurrences in the histological regression, and thus they consider that the use of topical 5% IMQ is an important therapeutic option for vulvar HPV-induced lesions.

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