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Imiquimod 5% cream versus cold knife excision for treatment of VIN 2/3: a five-year follow-up

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Abstract. – BACKGROUND: Vulvar intraepithelial neoplasia (VIN) is a premalingnant condition. For long time, surgery was considered the first-line therapy in the treatment of high grade VIN. Imiquimod was recently introduced as an alternative to surgery.

AIM: To compare the overall complete response, the recurrence rate and the risk factors for relapse among patients with VIN 2/3 treated with Imiquimod or surgical excision.

PATIENTS AND METHODS: Eighty women who had histological diagnosis of VIN 2 and VIN 3 were enrolled in this prospective study. Patients immunocompromised, with recurrent VIN, with well differentiated type VIN or VIN 1 and women treated more than once were excluded from the study. Patients were divided into two groups: group A was treated with Imiquimod, group B underwent surgical excision. Patients' characteristics analyzed were: age, smoking, degree of the primary lesion, state of margins, multifocal disease. We have evaluated the recurrence rate, the relapse rate, and the overall complete response, considering as recurrence the onset of a lesion after an initial complete response to Imiquimod and/or after the surgical treatment and as relapse all patients who had a recurrence plus those with medical treatment failure.

RESULTS: Multifocal lesions (p = 0.03) and VIN 3 (p = 0.002) were associated with a higher risk of relapse. The recurrence rate was higher in the group B (p = 0.009), but the relapse rate was higher in the group A (p = 0.04). The overall complete response was better in the group B (p = 0.04).

CONCLUSIONS: Although the advent of new medical options can decrease the morbidity associated with invasive surgical procedures, surgical treatments remain the best treatment modality for VIN with regard to relapse and overall complete response.

Key Words:
Imiquimod, Cold knife excision, VIN, Recurrence, Overall complete response.

Introduction

Vulvar intraepithelial neoplasia (VIN) is a premalignant lesion and a precursor of vulvar carcinoma. Traditionally VIN was classified into three grades, basing on the thickness involvement of the epithelium by dysplasia. In 2004 the International Society for the Study of Vulvolvaginal Disease classified VIN in two groups: usual type and differentiated type[1]. The two types differ in epidemiology, pathogenesis, clinical manifestation and malignant potential. Usual VIN commonly occurs in younger women, it is associated with human papillomavirus, of which HPV-16 subtype is most commonly isolated, and tends to have multicentric and multifocal involvement[2-5]. For long time, surgery was considered the first-line therapy in the treatment of high grade VIN[6]. However, surgical treatments often lead to sexual dysfunction and anatomical distortions. Furthermore, the usual type VIN is more commonly diagnosed in younger women because of the spread of HPV infection. In addition surgery does not clear the persistent infections, leading to frequent recurrences after treatment[7,8]. Imiquimod cream is an immune response modulator which produces the activation of innate immunity[9], so increasing viral clearance and remission of the lesion. The topical treatment with Imiquimod is safe and effective in the treatment of external

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genital warts caused by HPV, and it was recently introduced as an alternative for surgery in the treatment of vulvar and vaginal intraepithelial neoplasia[2,10].

The aim of this report was to compare the overall complete response, the recurrence rate and the risk factors for relapse among patients with high grade VIN treated with Imiquimod and patients undergoing surgical excision.

Patients and Methods

Since 2000 to 2012, from all the Universities and Country Hospitals participating in the study, a total of 80 women having histological diagnosis of VIN 2 and VIN 3 were enrolled in this prospective study. All the women gave their informed written consent.

The histological specimen was obtained by biopsy of a suspicious lesion. The histological diagnosis of VIN usual type was made according to the recently revised VIN terminology proposed by the International Society for the Study of Vulvovaginal Disease (ISSVD). Immunocompromised patients, those with recurrent VIN, or with well differentiated type VIN or VIN 1 lesions, and women treated more than once were excluded from the study. In order to evaluate the outcomes of different treatment modalities, patients were divided into two groups: 40 women underwent surgery, the other 40 were treated with Imiquimod. Surgery was performed by cold knife excision with 5 mm of free-margin. Imiquimod 5% (250 mg) was applied locally by the patient twice a week for 16 weeks (one cycle of therapy)[11]. All patients were seen every 6 months for a 5-year-follow-up. Women treated with Imiquimod who had a partial response (persistent but reduced-size lesion) after the first cycle underwent a second cycle in order to achieve a complete response. Patients treated with Imiquimod who relapsed or did not respond or had a partial response after 2 cycles were treated surgically. Among women treated with Imiquimod, we considered complete responders those who eliminated the lesion after 1 or 2 cycles; partial responders those who had a persistent but reduced-size lesion after 2 cycles; no responders those who had still the lesion unchanged after 1 cycle. In order to evaluate which kind of treatment offers the best outcomes, recurrence and relapse rates were evaluated. We have considered as recurrence the onset of a lesion after an initial complete response to Imiquimod and/or after the surgical treatment. We have considered as relapse all patients who had a recurrence plus those with medical treatment failure (no response or partial response to Imiquimod). The following patients' characteristics were analyzed, so evaluating if one of these increases the risk of relapse: age, smoking, degree of the primary lesion, state of margins, multifocal disease.

Statistical Analysis

Statistical analysis was performed with statistical program/SPSS for Windows, version 10 (SPSS Inc., Chicago, IL, USA). Continuous outcome variables were analyzed using the Student's *t* test. Discrete variables were analyzed using the Chi Square Test. The risk was assessed by calculating the Relative Risk (RR), with Confidence Intervals (CI) 95%.

Results

In the group of patients undergoing surgery, four were lost to follow-up, while among patients treated with Imiquimod two were lost to follow up and 6 were ruled out from the study because of the onset of side effects which did not allow to continue the treatment. So, 32 women treated with Imiquimod (group A) and 36 women treated with surgery (group B) were analyzed.

The mean age of group A was 42.6, the median age was 41.5. Non smokers were 43.7% (14/32), and smokers 56.3% (18/32). The degree of the initial lesion was VIN2 in 18.7% (6/32), VIN3 in 81.2% (26/32). Unifocal lesions were 21.8% (7/32), multifocal lesions were 78.2% (25/32). Multicentric lesions were observed in 50% of these patients: CIN was found in 34.3% of cases (11/32), and VaIN in 15.7% of cases (5/32). Recurrence rate was 15.6% (5/32), relapse was 68.7% (22/32). Mean time of recurrence was 25.6±19 months. Overall complete response was 31%. The surgical conversion rate was 53% (17/32). Among patients treated with Imiquimod, 13 had a complete response after the first cycle; ten showed a partial response, of which two responded completely after the second cycle, and the other eight underwent surgery. Nine showed no response, so they shifted to surgical treatment. Five patients relapsed after a complete response, of which three patients showed a complete response after one cycle, and the other two gained a complete response after two cycles. Two women developed an invasive cancer.

The mean age of group B was 40.1 years, the median age was 39.5. Non smokers were 47.3% (18/38) and smokers 52.7% (20/38). The degree of the initial lesion was VIN2 in 39.4% (15/38) and VIN3 in 60.6% (23/38). Unifocal lesions were 28.9% (11/38), multifocal lesions were 71.1% (27/38). Multicentric lesions were observed in 42% of these patients: CIN was found in 36.8% of cases (14/38) and VaIN in 5.2% of cases (2/38). Margins were negative in 73.6% of patients (28/38) and positive in 26.4% of patients (10/38). Three patients developed invasive cancer. Recurrence rate was 44.7% (17/38). Mean time of recurrence was 29±26 months. Overall complete response was 55%. The presence of multifocal lesions ($p = 0.03$) and VIN 3 ($p = 0.002$) before treatment were associated with a higher risk of relapse, while smoke ($p = 0.6$) and multicentric lesions ($p = 0.6$) did not increase the risk. Any significant statistical difference was found comparing age of patients with relapse and those without ($p = 0.4$). The recurrence rate was higher in the group B ($p = 0.009$), but the relapse rate was higher in the group A ($p = 0.04$). The overall complete response was better in the group B ($p = 0.04$).The main results are summarized in Table I.

Discussion

The incidence of VIN is increasing worldwide, above all in younger women up to age 40 to 49 years[12]. The management options are multiple testifying to the fact that none of them is truly satisfactory as the various treatments are notorious for high failure and recurrence rate. Treatment protocols use surgical excision procedures, ablation ones and a variety of off label medical therapies such us 5% 5-Fluorauracil, and most recently self-applied immunotherapy with 5% imiquimod cream. The latter seems to be particularly suitable for the majority of HPV related VIN occurring in younger women in whom preservation of lower genital anatomy is crucial[13].

In recent years, randomized control trials have shown that the application of 5% imiquimod is effective in the treatment of high-grade VIN, and have evaluated the response and the recurrence rate with this treatment[11,14-17]. But these first studies had a short term follow-up, so presenting important bias because of the high risk of recurrence even after several years from the primary treatment[18]. Recently, Terlou et al[19] published a report which considered seven-years median follow-up showing that in case of complete response, imiquimod is effective in the long term. However, all the investigations compared the patients treated with imiquimod to a control group treated with placebo, and only few authors analyzed data about the main outcomes in women treated with imiquimod and in women treated with different modalities[13,20,21].

The current work compared the outcomes of surgery and treatment with imiquimod in terms of overall complete response, number of relapses and recurrences. The results obtained demonstrate that during 5 years follow-up, the overall complete response achieved was higher in patients treated with surgery ($p = 0.04$). The recurrence rate was lower in women treated with imiquimod ($p = 0.009$), but this datum does not account for non responders to imiquimod who shifted to surgery. Considering as main outcome both recurrence rate and surgical conversion rate, the surgical treatment has proven to be more effective than imiquimod. Our results support previous studies which also found relatively high failure and recurrence rates in patients treated with imiquimod, compared to primary local excision[13,22].

Table I. Risks factors for relapse and treatment outcomes.

Risk factors	RR (95% CI)	*p* value		Imiquimod n (%)	Surgery n (%)	*p* value
Age		0.44	Recurrence	5/32 (15.6)	17/38 (44.7)	0.009
Smoke	0.86 (0.49-1.50)	0.6	Relapse (recurrence plus treatment failure)	22/32 (68.7)	17/38 (44.7)	0.04
Margins	3.10 (1.86-5.16)	0.001				
Multifocality	2.28 (0.93-5.59)	0.03	Overall complete response	10/32 (31)	21/38 (55)	0.04
Multicentric lesions	1.13 (0.72-1.75)	0.6	Disease free	25.6 ± 19 months	29 ± 26 months	0.6
Degree (VIN3)	2.36 (1.17-4.76)	0.002				

Having excluded from the research immune-compromised women, which generally have a lower response rate to imiquimod treatment, this study is devoid of this kind of bias.

Although the surgical treatments are the mainstay of management of VIN, VIN recurs in 30-50% of cases, above all if excision margins are positive[23]. Indeed, also from our data it appears that positive surgical margins are an important risk factor for relapse.

In our report other factors that seem to be associated to major risk of relapse are the presence of multifocal lesions. In accord with other investigations[7,21], and the degree of VIN before treatment. Smoke is well known to be associated with the incidence of VIN[8], and also with the relapse/recurrence rate[8,21]. However, our research did not report the association between smoke and relapse/recurrence rate, as other authors[24]. Even if the presence of multicentric disease has been reported by Kuppers et al[25] to be associated with the relapse, we did not achieve the same result. Finally also the age was not found to be associated to relapse.

Even if women with VIN should be considered at risk of recurrences and vulvar cancer throughout their lifetimes, the rate of progression seems to be slow. So, data from the literature suggest that women with a complete response to therapy and no new lesions at 6 and 12 months after initial treatment should be monitored annually thereafter[23].

Although the advent of new medical options can decrease the morbidity associated with invasive surgical procedures, surgical treatments remain the principal treatment modality for VIN with regard to relapse and overall complete response. Because of the viral-related nature of usual VIN, the therapy should cover broader areas to treat occult multifocal disease and ensure HPV is cleared. Less data exist with respect to combination therapy. It would be suitable to analyze the outcomes of combination therapies, e.g. imiquimod plus surgery, in order to act on both the macroscopic lesion removal and immune response to the virus. To date a single study has compared single treatments and combination ones, founding contrasting results[21].

It is clear that the current treatments for VIN are suboptimal. The best approach is toward individualization management based on clinical presentation, extent of disease and patient preference. Another possible advise is the vaccine. The use of quadrivalent vaccine has been shown to decrease the risk of VIN and should be recommended for women in target population[26].

Conclusions

Although the advent of new medical options can decrease the morbidity associated with invasive surgical procedures, surgical treatments remain the best treatment modality for VIN with regard to relapse and overall complete response.

Conflict of Interest

None.

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