Research Article

Treatment of Residual or Recurrent CIN with Topical Imiquimod: a Retrospective Study

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Abstract

Objective

In this retrospective case study, we determine the results, side effects and long-term outcome features of treatment with imiquimod 5% in women with recurrent or residual cervical intraepithelial neoplasia (rrCIN).

Methods

The study was set in three outpatient clinics of hospitals in the Netherlands. Women diagnosed with rrCIN and treated with imiquimod 5% intravaginally between 2010 and up to and including 2017 were included. Data were extracted from medical records. The main outcome measures were complete regression or partial regression of SIL (squamous intraepithelial lesions) (cytology) or CIN (histology), side effects and long-term outcome in terms of the need for further excisional treatment during the follow-up period. Outcomes were assessed using descriptive statistics.

Results

The 18 studied women tolerated imiquimod well: all completed the treatment, with a temporary stop or dose reduction in two. The treatment was successful in 11 women overall (61%) of whom 8 women (80%) with high grade CIN (grades II-III). Of these 11 women, 4 women developed a recurrence of which 3 women were treated successfully with imiquimod or a LLETZ procedure. One woman died in the follow up without treatment of the CIN lesion. Of the remaining seven women with unsuccessful treatment, four patients underwent additional therapy. Two women underwent a hysterectomy, one woman underwent multiple procedures and the last woman underwent laser therapy and imiquimod, but died in the follow up. Of the remaining three out of those 7 women with unsuccessful treatment, two women refused further therapy and one woman required no further therapy since she cleared HPV and showed no dysplasia in the follow-up period.

Conclusions

In studied population, imiquimod treatment was well tolerated and associated with resolution or regression of SIL/CIN in 61% of women. We have started a randomized controlled trial to compare the efficacy of imiquimod with that of LLETZ in recurrent or residual CIN.

Keywords

Cervical intraepithelial neoplasia; Imiquimod; Human papillomavirus; Prevention cervical cancer; Cervical dysplasia; LLETZ; Transformation zone

Introduction

Cervical cancer ranks as the fourth most frequently diagnosed cancer type and it is the fourth leading cause of cancer death in women worldwide [1]. Cervical intraepithelial neoplasia (CIN) is the precursor of cervical cancer and develops mostly in women of reproductive age. CIN is classified into low grade squamous *intraepithelial* dysplasia (CIN 1) and high grade squamous *intraepithelial* dysplasia (CIN 2-3). CIN 1 is almost universally left untreated because the probability of progression to cervical cancer is low and the lesion usually resolves spontaneously. CIN 2 and CIN 3, however, are considered precursors of cervical cancer and therefore usually treated with a 'large loop excision of the transformation zone' (LLETZ) [2]. This is a surgical procedure aimed at eliminating the affected part of the transformation zone. This procedure has potential complications such as hemorrhage, infection and complications in subsequent pregnancies. Multiple studies have shown a higher risk of premature birth among women who have undergone a LLETZ procedure [3-5]. This risk even reaches up to 13% among women who underwent more than one treatment procedure [6].

Disease residue or recurrence after a first LLETZ procedure occurs in 10-15% of cases [7]. A second LLETZ procedure is usually performed if this concerns a CIN 2-3 lesion [2]. Because of the higher risk of premature birth after multiple LLETZ procedures, it might be commendable to apply non-invasive treatment in young patients with residual or recurrent CIN (rrCIN).

One of the possibilities is the application of imiquimod cream. This topical immune response modifier with indirect antiviral and antitumor properties is commonly used to effectively treat genital warts and basal cell carcinoma [8]. Yet, it has also been found effective in the treatment of primary CIN lesions: in a randomized controlled trial, disease regression of high grade CIN was found in 73% of women treated with a 16-week course of intravaginal imiquimod cream [9]. Evidence on the efficacy of imiquimod in the treatment of rrCIN is largely lacking; only one

study has reported on the treatment of rrCIN with imiquimod [10]. This was a case series from Diaz-Arrastia et al including two HIV-positive women treated with imiquimod after failed LLETZ or cryotherapy; neither had needed additional surgical therapy during 22.5 –months follow-up.

To obtain more evidence about the use of imiquimod in rrCIN, we retrospectively studied efficacy and safety of imiquimod therapy in patients with residual or recurrent CIN after previous excisional treatment.

Methods

Study Design

This retrospective case study concerned patients treated in three hospitals in the Netherlands; Meander Hospital in Amersfoort, the Erasmus University Medical Center in Rotterdam, and Havenziekenhuis in Rotterdam. After Grimm and colleagues [9] had demonstrated the beneficial effect of imiquimod in patients with cervical dysplasia, this treatment modality was offered off label in selected cases in these hospitals. The study was approved by the Medical Ethics Review Board of the Erasmus University Medical Center (MEC-2015-035). There was neither patient nor public involvement in this retrospective study. The study was not funded.

We included all women with histological or cytological proven rrCIN after previous surgical treatment, who were subsequently treated with imiquimod, between 2010 up and including 2017. Because of the retrospective data and the heterogeneity of the study group, it was impossible to differentiate between a recurrent or a residual lesion.

Relevant data of these patients were retrieved from their medical records.

Treatment Procedures

The included patients had received suppositories of imiquimod cream 5% for 16 to 24 weeks, and had inserted the cream intravaginally two to three times a week. One patient had applied the cream on a vaginal tampon. If side effects were noted, the frequency could be reduced or medication could temporarily be stopped. Any side effects had been recorded in patient's file.

Data extracted from the medical record included the reason for the use of imiquimod, the obstetric and medical histories; other human papillomavirus (HPV) related diseases, CIN classification of the previous primary treatment, CIN grade at the start of imiquimod treatment, and side effects of the treatment. The primary outcome of this study was efficacy of the imiquimod treatment, defined as a cytological or histological regression of the lesion – either partial of complete. Partial regression was defined as a lower CIN classification based on cytology or histology at the first follow-up visit after initiation of imiquimod treatment in comparison to the baseline classification. Complete regression was defined as the absence of dysplasia on histology or cytology at the first follow-up visit. No regression was defined as no change or a higher grade of dysplasia on histology or cytology at the first follow-up visit in comparison to the baseline grade. Conversion of HPV-positive status to HPV-negative status, the side effects of imiquimod and the long-term outcome in terms of the need for further excisional treatment during the follow-up period were monitored.

Statistical analysis was performed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were applied to patient characteristics and the primary outcome measure. Fisher`s exact test was applied for analysis of subgroups. All p-values are two-sided and significance was set at $P < 0.05$.

Results

Population Characteristics

Eighteen women treated for rrCIN with imiquimod in the eight-year period under study were included in this study. Their baseline characteristics are listed in table 1. The median age was 37.7 years (range 28-71 years). Five women were immunocompromised, four of whom used immunosuppressive medication (infliximab, tacrolimus, azathioprine, prednisone, mycophenolatemofetil). One of these five patients was infected by HIV. The primary treatment indication had been CIN 2 or CIN 3 in the majority of patients (89%); and the treatment consisted of LLETZ in 15 women (83%) and conization in three women (17%). Nine women had undergone more than one excisional treatment procedures before treatment with imiquimod.

Imiquimod Treatment Indications, Procedures and Side Effects

Specifications on imiquimod treatment indications and procedures can be found in table 2. The rrCIN grade prior to imiquimod treatment was moderate to severe in ten women and borderline or mild in eight women. Seven women's HPV status before imiquimod treatment had not been assessed; the status of the other eleven women was high risk HPV positive.

The commonest reasons for the treatment with imiquimod were a future pregnancy wish (22%), concomitant vaginal intraepithelial neoplasia (VaIN) lesions (22%) and impossibility to perform another excisional procedure due to insufficient cervical length (22%).

All patients had completed the treatment, although one had temporarily stopped applying imiquimod because of side effects and another patient had received a reduced dosage for the same reason. Of all patient-reported side effects, fatigue was most common (50%). Other frequently noted side effects were headache, vaginal pain, myalgia and fever. Physician-reported side effects were vaginal redness (one patient) and temporary elevation of liver enzymes (one patient). One patient had a vaginal erosion until 6 months after stopping the treatment.

Treatment Outcomes

Table 3 shows treatment specifications and outcomes per patient. The first examination after treatment was cytology in 10 women; colposcopy and biopsies in seven women; both cytology and colposcopy with biopsies in one woman. The time passed between the end of the imiquimod treatment and the first exam varied from 2 weeks to 26 weeks. The treatment was considered successful in 11 patients (61%); i.e. complete regression (n=7) or partial regression of the CIN grade (n=4), as shown on histology or cytology after treatment. Six patients (33%) had stable disease. One patient (6%) showed disease progression after the treatment with imiquimod and underwent laser treatment because she also had VaIN lesions.

Table 1. Patients' baseline characteristics (n=18)

Characteristics	
Age (yrs)	
Median	37.7
Range	28-71
Parity	
0	10
1	3
2	1
3	2
4	1
missing	1
Smoking status (No. of patients)	
Smoking	4
Non-smoking	10
Recently quit smoking (<3 months)	1
Unknown	3
Immunodeficiency or immunosuppressive medication	
Yes	5
No	13
Number of ablative/excisional treatments before treatment with imiquimod	
1	9
2	6
3	3
Method of first excisional treatment in history (No. of patients)	
LLETZ procedure	15
Cold knife conization	3
Grade of dysplasia in first excisional treatment ((No. of patients (%))	
CIN 1	2 (11%)
CIN 2	5 (28%)
CIN 3	11 (61%)
Other HPV-related disease (No. of patients)	
VIN	1
VAIN	6
AIN	0
Genital warts	4

LLETZ: Large Loop Excision of the Transformation Zone, CIN: cervical intraepithelial neoplasia, VIN: Vulvar Intraepithelial neoplasia, VaIN: Vaginal Intraepithelial neoplasia, AIN: Anal Intraepithelial neoplasia

Table 2: Imiquimod treatment characteristics (n=18)

Grade of dysplasia (cytological or histological) before treatment (No. of patients (%))	
Borderline or mild	8 (44%)
Moderate	5 (28%)
Severe	5 (28%)
Hr-HPV status before treatment with imiquimod	
Positive	11
Negative	0
Unknown	7
Reason for use of imiquimod (No. of patients)	
Wish to conceive in the future	4
Concomitant VaIN lesions	4
No cervical length for LLETZ procedure	4
Multiple LLETZ procedures in history	3
Comorbidity	1
Long-lasting low grade abnormal cytology	1
Unknown	1
Application (No. of patients)	
Suppositories	17
Tampon	1
Duration of treatment (weeks)	
16 weeks	14
17 weeks	1
24 weeks	2
Unknown	1
Time passed between first abnormal cytology after primary treatment and start of treatment with imiquimod (months)	
Median	19
Range	2-69
Side effects ((No of patients (%))	
Fatigue	9 (50%)
Headache	6 (33%)
Pain	5 (28%)
Myalgia	4 (22%)
Fever	4 (22%)
Discharge	3 (17%)
Itching	2 (11%)

Hr=high risk

The outcomes of subgroup analyses regarding the association between patient characteristics and treatment efficacy are reported in table 4. Immunodeficiency, number of previous treatment procedures, smoking and parity did not seem to be associated with treatment efficacy. A potential association was found for treatment interval, age and disease grade, although not statistically significant. We found a trend for better treatment response in patients in whom rrCIN had persisted for less than a year in comparison with patients with a longer duration of rrCIN (80% vs 64%; p value 0.60). The same holds for patients younger than 35 years versus older patients (86% vs 45%; p value 0.15) and for women with high grade CIN compared with women with low grade CIN (80% vs 38%; p value 0.145).

The median long-term follow-up period was 26 months (range 0-95 months) and is described in table 5. One (patient 8) of the seven women who had no dysplasia after imiquimod treatment developed recurrence of disease. She then underwent a LLETZ procedure, after which cytology results were normal.

Recurrence had occurred in three of the four patients with partial regression. One patient (patient 4) received imiquimod again, which was successful (complete regression). The other (patient 12) underwent a LLETZ procedure and started imiquimod immediately after the procedure. She still has abnormal cytology in 2019, however, and has been advised to undergo another surgical procedure. Cytology findings remained abnormal in the third patient (patient 17) whose lesion had regressed, but she refused therapy. She had a history of kidney transplantation and diabetes and died of pneumonia 2.5 years after the imiquimod treatment.

One of the three patients (patient 6) with a stable disease and an expectative management underwent a LLETZ procedure twice after the imiquimod treatment. One (patient 9) other underwent a LLETZ and later a hysterectomy. Yet another (patient 15) underwent a hysterectomy after a long period of abnormal cytology results.

The disease had recurred after laser therapy in the one patient with progression of disease (patient 5). She then was treated with imiquimod again. Shortly after completing the treatment, she died of the complications of autoimmune hepatitis and liver transplantation, which was unrelated to the use of imiquimod (Table 5).

Although not being a primary endpoint, hr-HPV status was also monitored. Seven of the 15 patients who had been tested for hr-HPV after treatment were tested negative (47%). Four of these seven women had a proven HPV infection before imiquimod treatment and thus had cleared this. The prior-to-treatment HPV status of the other three was unknown.

Table 3: Outcome per patient (n=18)

Patient	Grade of dysplasia at first treatment	Number of previous surgeries	Grade of dysplasia at start study	Time passed between completing treatment and first follow up	Outcome of first follow up	Complete regression/partial regression/no regression
1	CIN 3	1	CIN 3	unk	No dysplasia (cyt)	Complete regression
2	CIN 3	2	CIN 3	10 weeks	No dysplasia (cyt+hist)	Complete regression
3	CIN 3	1	Severe dysplasia (cyt)	2 weeks	No dysplasia (cyt)	Complete regression
8	CIN 3	2	CIN 1	14 weeks	No dysplasia (cyt)	Complete regression
10	CIN 3	3	CIN 3	12 weeks	No dysplasia (cyt)	Complete regression
13	CIN 2	1	CIN 1	14 weeks	No dysplasia (hist)	Complete regression
18	CIN 2	2	CIN 2	unk	No dysplasia (hist)	Complete regression
4	CIN 2	1	CIN 2	4 weeks	Borderline dysplasia (cyt)	Partial regression
11	CIN 3	1	CIN 2	4 weeks	CIN 1	Partial regression
12	CIN 3	2	CIN 3	12 weeks	CIN 2	Partial regression
17	CIN 3	2	CIN 3	9 weeks	CIN 1	Partial regression
6	CIN 3	1	CIN 2	26 weeks	Moderate dysplasia (cyt)	No regression
7	CIN 3	3	Borderline dysplasia (cyt)	24 weeks	Moderate dysplasia (cyt)	No regression
9	CIN 2	1	CIN 2	8 weeks	CIN 2	No regression
14	CIN 2	1	CIN 1	8 weeks	Mild dysplasia (cyt)	No regression
15	CIN 1	1	CIN 1	12 weeks	Mild dysplasia (cyt)	No regression
16	CIN 1	2	CIN 1	11 weeks	Mild dysplasia (cyt)	No regression
5	CIN 3	3	CIN 1	8 weeks	CIN 2	No regression

cyt:Cytology, hist:Histology

Table 4: Patient characteristics in relation to successful outcome (n=18)

	Successful treatment	P value
All patients	11/18 (61%)	
Immunodeficiency		
Yes	3/5 (60%)	1.000
No	8/13 (62%)	
Time passed between diagnosis of rrCIN and start of imiquimod treatment		
<1 year	4/5 (80%)	0.596
≥1 year	7/13 (64%)	
Patient's age at start of imiquimod treatment		
≤35 year	6/7 (86%)	0.151
>35 year	5/11 (45%)	
Lesion grade at start of imiquimod treatment		
Low grade lesion	3/8 (38%)	0.145
High grade lesion	8/10 (80%)	
Number of surgical treatments before start of imiquimod treatment		
1	5/9 (56%)	1.000
>1	6/9 (67%)	
Parity		
Nulliparous	6/10 (60%)	1.000
One of more children	4/7 (57%)	
Smoking		
Yes	3/5 (60%)	1.000
No	6/10 (60%)	

Table 5: Overall information per patient (supplement) n=18

Pt	Grade of dysplasia at first treatment	Number of previous surgeries	Grade of dysplasia at start study	Hr-HPV status start study	Time passed between completing treatment and first follow up	Outcome of first follow up	Outcome at end follow up	Hr-HPV status after treatment	Long-term follow–up outcome
1	CIN 3	1	CIN 3	pos	unk	No dysplasia (cyt)	CR	unk	Lost after first follow up
2	CIN 3	2	CIN 3	pos	10 weeks	No dysplasia (cyt+hist)	CR	neg	No treatment, no dysplasia in follow up
3	CIN 3	1	Severe dysplasia (cyt)	unk	2 weeks	No dysplasia (cyt)	CR	neg	No treatment, no dysplasia in follow up
8	CIN 3	2	CIN 1	pos	14 weeks	No dysplasia (cyt)	CR	unk	Recurrence 1x LLETZ, afterwards normal cytology
10	CIN 3	3	CIN 3	unk	12 weeks	No dysplasia (cyt)	CR	pos	No treatment, no dysplasia and HPV negative in follow up
13	CIN 2	1	CIN 1	pos	14 weeks	No dysplasia (hist)	CR	neg	No treatment, no dysplasia in follow up
18	CIN 2	2	CIN 2	unk	unk	No dysplasia (hist)	CR	neg	No treatment, no dysplasia and HPV negative in follow up
4	CIN 2	1	CIN 2	unk	4 weeks	Borderline	PR	neg	Recurrence, treated

						dysplasia (cyt)			with imiquimod, afterwards no dysplasia and HPV negative
11	CIN 3	1	CIN 2	pos	4 weeks	CIN 1	PR	neg	No treatment, no dysplasia and HPV negative in follow up
12	CIN 3	2	CIN 3	unk	12 weeks	CIN 2	PR	pos	In follow up LLETZ and imiquimod combined, persistent dysplasia for which 4th LLETZ scheduled
17	CIN 3	2	CIN 3	pos	9 weeks	CIN 1	PR	pos	Recurrence of high grade dysplasia, died because of pneumonia
6	CIN 3	1	CIN 2	unk	26 weeks	Moderate dysplasia (cyt)	NO	pos	First follow up, 2x LLETZ, afterwards normal cytology HPV negative
7	CIN 3	3	Borderline dysplasia (cyt)	pos	24 weeks	Moderate dysplasia (cyt)	NO	neg	No treatment, normal cytology HPV negative
9	CIN 2	1	CIN 2	pos	8 weeks	CIN 2	NO	pos	Immediate LLETZ procedure,

									hysterectomy due to persistent dysplasia (CIN 3)
14	CIN 2	1	CIN 1	pos	8 weeks	Mild dysplasia (cyt)	NO	pos	Persistent low grade dysplasia, refuses treatment
15	CIN 1	1	CIN 1	pos	12 weeks	Mild dysplasia (cyt)	NO	unk	Abnormal cytology, hysterectomy (no dysplasia found)
16	CIN 1	2	CIN 1	pos	11 weeks	Mild dysplasia (cyt)	NO	pos	Persistent low grade dysplasia, refuses treatment
5	CIN 3	3	CIN1	unk	8 weeks	CIN 2	PO	pos	Immediate laser, persistent dysplasia for which imiquimod. Died due to auto-immune hepatitis

Pt: Patient, CR: Complete regression, PR: Partial regression, NO: No regression, PO: Progression, pos: Positive, neg: Negative, unk: Unknown, cyt: Cytology, hist: Histology

Discussion

This is the first study on efficacy of imiquimod treatment for women with residual or recurrent CIN lesions. The treatment had the desired effect in 11 of the 18 women studied (61%). Imiquimod was well tolerated and all patients completed the prescribed treatment.

Patient 7 was defined as stable disease and unsuccessful treatment, since our primary outcome was defined as histological or cytological regression of the lesion. However, despite the stable disease, there was clearance of HPV and complete regression in all cytology afterwards. Clinically this could be seen as successful treatment, which would bring our success rate up to 67%.

Imiquimod treatment of women with proven rrCIN has been described for only two cases [10]. Both women in this study were infected with HIV and both responded well to imiquimod. Still, one of them needed a second treatment with imiquimod. Compared to this data, in our study the response to imiquimod treatment did not differ between the women who were immunocompromised and the women who were not immunocompromised.

An overall 61% success rate of imiquimod treatment may seem moderate, but the efficacy of an additional LLETZ procedure instead of imiquimod treatment may not necessarily be better. One previous study that compared LLETZ versus laser cone biopsy for secondary excision for CIN, showed a high recurrence rate after secondary LLETZ treatment [11]. In the LLETZ group, 59% of the women had normal follow up cytology after 12 months. This would imply that LLETZ is possibly not superior to imiquimod in the treatment of rrCIN. However, since sample sizes are small in that study and our study, and the outcome measures may not be comparable, additional research is necessary to conform this supposition.

Based on the retrospective evaluation of 18 women in this study, the treatment efficacy of imiquimod in rrCIN seems to be lower than the treatment efficacy in primary lesions [9]. A plausible explanation is the fact that rrCIN represents more aggressive or extensive disease. In our study, seven of the 15 patients who had been tested for hr-HPV after treatment, were tested negative (47%). This percentage is lower than the 90% reported by Chen et al [12]. The study of Chen, however, is not comparable to our study, since in this study not all women necessarily had a rrCIN lesion. Women who remained HPV positive directly after the LLETZ procedure were included in the study and treated with imiquimod. The spontaneous regression rate in the population in that study may have been higher than the regression rate in our study.

We found that imiquimod was relatively well tolerated, although side effects were not uncommon. The frequency and nature of these side effects were comparable to the frequency and nature of the side effects reported in previous studies in which women were treated with vaginal imiquimod [9]. Nevertheless, all patients completed the treatment, albeit that one woman had temporarily stopped treatment and for one woman the dose had been reduced. The high compliance with treatment can probably be ascribed to earlier treatment failure – and thus high motivation to complete treatment.

An interesting finding of our study is that imiquimod treatment was not confined to women with a future pregnancy wish. In a previous study [13], we found that especially patients with the wish to conceive would be willing to see imiquimod as a treatment option for CIN, with the

aim to reduce the risk of premature birth after repeated LLETZ treatment. In the present study, however, in women already treated for CIN, we see a broader spectrum of indications. This could mean that in the future more of the women already treated for CIN would be interested in treatment with imiquimod.

Strengths and limitations

The main strength of this study is that it has yielded useful information about the efficacy of imiquimod treatment in women with rrCIN, which information can be used in patient counselling. Furthermore, the long follow-up period permitted monitoring of the recurrence of CIN after completing the treatment. Major limitations of this study are the possible inclusion bias. Since there was no randomization, it could be that women with certain characteristics were selected for treatment. There were also missing data, inherent to the retrospective nature of the study. As our study was a multicenter study, their treatment durations and the ways to apply the medication varied.

Interpretation

There is limited evidence on the efficacy of imiquimod treatment in patients with rrCIN. We found that this treatment was successful in 61% of the study population and was generally well tolerated, with side effects comparable to those reported in previous studies on intravaginal imiquimod. Besides a future pregnancy wish, there may be other reasons to choose imiquimod treatment over a repeated LLETZ procedure.

Conclusion

In this retrospective case study, imiquimod treatment was associated with absence or regression of 61% of included women with rrCIN. Not much is known about the success rate of the standard treatment, a secondary LLETZ procedure. We therefore have started a randomized controlled trial comparing imiquimod treatment with a secondary LLETZ procedure in patients with residual and recurrent CIN lesions, the TopIC-2 study (ClinicalTrials.gov **NCT02669459**).

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Disclosure of Interests

The authors declare that they have no conflict of interests.

Contribution to Authorship

AvdS, MK, CG, AJK, FvK and HvB designed the study. AvdS collected the data. AvdS, RvB and HvB analysed the data. AvdS, MK, RvB and HvB drafted the manuscript. All authors actively participated in interpreting the results and revising the paper and all authors approved the final manuscript.

Details of Ethical Approval

Approved by the Medical Ethics Review Board of the Erasmus University Medical Center Rotterdam (MEC-2015-035), 20th January 2015.

Abbreviations

CIN: Cervical Intraepithelial Neoplasia

LLETZ: Large Loop Excision of the Transformation Zone

HPV: Human Papillomavirus

VIN: Vulvar Intraepithelial Neoplasia

VAIN: Vaginal Intraepithelial Neoplasia

AIN: Anal Intraepithelial Neoplasia

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