

Keratinocyte Carcinoma Chemoprevention With a Combination of Imiquimod, 5-Fluorouracil, and Tretinoin

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ABSTRACT

Background: The incidence of keratinocyte carcinomas (KCs), comprising basal and squamous cell carcinomas, is rising in the United States. Chemoprevention is one modality by which patients can reduce the incidence of KCs.

Methods: We performed a retrospective review of 327 patients who employed a combination of imiquimod 5% cream, 5-fluorouracil 2% solution, and tretinoin 0.1% cream in a field therapy regimen over the face/ears or scalp for chemoprevention.

Results: Patients had dramatically lower odds of having KCs in the treatment location (face/ears or scalp) in the one-year period after field treatment than in the one-year period preceding field treatment (OR=0.06, 95% CI: [0.02, 0.15]). Patients were also at lower odds of having KCs in non-treated areas the year after field treatment than in the year preceding it (OR=0.25, 95% CI: [0.14, 0.42]). Additionally, fewer cryotherapy sessions were performed for actinic keratoses in the treatment areas in the year after treatment (mean=1.5, SD=1.21) than the year preceding treatment (mean=2.3, SD=0.99; t=11.68, P<0.001).

Conclusions: A combination of imiquimod 5% cream, 5-fluorouracil 2% solution, and tretinoin 0.1% cream were effective at reducing the incidence of new KCs for at least one year. Individualized treatment application frequency allowed for increased patient adherence. Prospective studies evaluating combination topical treatments for chemoprevention of KCs are needed to further assess the treatment effects found in this study.

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INTRODUCTION

Keratinocyte carcinomas (KCs), comprising basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), are the most frequently occurring human malignancies. Cure rates are high, but the incidence of KCs is on the rise in the United States.[1] Correspondingly, the costs to treat these KCs are also dramatically increasing.[2] In 2016, Chen et al examined the costs associated with invasive surgical treatment of skin cancer using the Medicare payment database. They reported a progressive increase in annual costs, amounting to a staggering 8.1 billion dollars in 2011.[3] In addition to the costs, there is substantial morbidity when treating these KCs. Surgery remains the standard of care because of high cure rates; however, surgery can be associated with pain, bleeding, infection, scarring, and prolonged recovery.[4,5] Chemoprevention is one method by which patients can reduce the incidence of malignant transformation to KCs.[6] Current chemoprevention strategies include topical aminolevulinic acid and methyl aminolevulinate with photodynamic therapy (PDT),[7,8] acitretin,[9] isotretinoin,[10] niacinamide,[11] COX-2 inhibitors,[12] human papillomavirus (HPV) vaccines,[13] topical 5-fluorouracil,[14] combinations of 5-fluorouracil and calcipotriol,[15] imiquimod cream,[16] tirbanibulin,[17] and chemical peels.[18]

However, additional modalities are needed as current methods remain costly and may still be associated with significant morbidity, poor patient adherence, and ineffectiveness. Examples include PDT,[8] systemic retinoids,[19] and oral COX-2 inhibitors.[20-22] One study showed a 2 to 4 week course of topical 5-fluorouracil 5% cream applied to the face and ears was found

to reduce SCCs for up to a year.[14] However, this 5-fluorouracil 5% cream course was not found to reduce the risk of BCCs. In previous studies of actinic keratoses (AKs), monotherapy with either imiquimod 5% cream or 5-fluorouracil 5% cream led to prolonged cutaneous irritation, with poor patient adherence in some cases.[23,24]

Given the rising incidence of KCs and resultant rising costs, there is a need for cost-effective and patient-centered options to prevent both SCCs and BCCs. Previous studies have shown that local application of a combination of imiquimod 5% cream, 5-fluorouracil 2% solution, and tretinoin 0.1% cream (IMI/5-FU/TRET) was able to effectively treat keratinocyte carcinomas (KCs)[45] and melanoma in situ.[25,26] Although patients were instructed to apply the combination 5 times per week for 6 weeks (42 days), excessive irritation from the combination sometimes led to poor patient compliance. When patients spread out the 30 applications over 76 days, compliance improved. Given the previously shown efficacy of this treatment, the present study sought to determine whether a similar combination of IMI/5-FU/TRET, employed as field therapy for AKs and applied 30 times within a 76-day treatment window, would provide effective chemoprevention against KCs both within and outside the treated areas. It was hypothesized that this prolonged treatment course (up to 76 days) with patient-controlled application frequency would increase patient adherence to the 30 treatments. We, therefore, present the results of a retrospective study on patients who employed the IMI/5-FU/TRET combination in a field therapy regimen over the face/ears or scalp to determine if patients had lower odds of having KCs in the in-field areas and out-of-field areas one year after completing the chemoprevention regimen.

MATERIALS AND METHODS

This study was approved by the University of Miami's Institutional Review Board using data from patients seen from October 1, 2016, to December 31, 2021, in a dermatology clinic. Patients who initiated chemoprevention for AKs and/or KCs were instructed to mix one whole packet of 5% imiquimod cream, 2 drops of 2% 5-fluorouracil solution, and one pea-size amount of tretinoin 0.1% cream in the palm of one's hand with a glove. Patients were instructed to apply the combination evenly to the face, including the posterior and anterior aspects of the ears, as well as for the non-hair-bearing areas of the scalp (typically in men). The application was performed 2 hours before bedtime. Patients were instructed to apply up to 30 applications of the combination at their discretion (at a maximum frequency of 5X/week for 6 weeks). Patients determined the frequency of the application to mitigate excessive irritation. Patients were instructed to apply liberal amounts of petroleum jelly between applications to reduce irritation. Patients were also monitored periodically and instructed to document their side effects.

All patients experienced varying degrees of local skin reactions, including erythema, scaling, burning, pain, and erosions. If side effects were not tolerable, patients could reduce the frequency of applications, stop the applications, or apply a course of clobetasol 0.05% cream twice a day for 2 to 3 days. At their discretion, patients could resume treatment with the goal of reaching 30 topical treatment applications.

We performed a retrospective study on patients who employed IMI/5-FU/TRET combination in a field therapy regimen over the face/ears or scalp. We identified 849 patients who initiated chemoprevention on the face/ears or scalp with combination therapy of IMI/5-FU/TRET. Inclusion criteria for our study included having an observation period of one year prior to the onset of chemoprevention therapy through one year after the cessation of the 30th application of the field treatment. Another criterion included completing the field chemoprevention treatment of 30 applications of the combination therapy within a 76-day period.

For each patient, we identified those who had at least one KC in the one-year period preceding the onset of chemoprevention field therapy and one year following the cessation of chemoprevention therapy. The occurrence of KCs was examined separately for KCs within the treatment area and KCs outside the treatment area. Moreover, we looked at the number of cryotherapy sessions needed for treating AKs one year before and one year after the completion of the chemoprevention course. In addition, the age of the patient, smoking status (never smoked, former smoker, current smoker), and whether the patient was immunocompromised were also recorded.

Statistical Analysis

Patients who had skin cancer in the area they received chemoprevention treatment (ie, face, ears, or scalp) were considered to have had an in-field occurrence, and those who had skin cancer outside the area they treated were considered to have had an out-of-field occurrence. Cancer occurrence was further stratified by type of cancer (ie, SCC, BCC, and melanoma); the stratified in-field treatment analysis was limited to SCCs and BCCs since there were no in-field occurrences of melanoma. Conditional logistic regressions were used to assess whether there were differences in in-field and out-of-field cancer occurrence in the year before treatment and the year after treatment. Conditional logistic regressions were selected due to the paired structure of the data. Additionally, a paired t-test was used to compare the mean number of cryotherapy sessions for AKs in the year before treatment and the year after treatment.

The sample was also stratified by smoking status into smokers and non-smokers. Analyses for in-field and out-of-field incidence and the number of cryotherapy sessions were repeated for the subgroups. Additionally, sensitivity analyses were conducted

TABLE 1.

General Characteristics of Patients With Keratinocyte Carcinomas in a Retrospective Review	
Characteristics	
Sex	*n* (%)
Female	147 (45)
Male	180 (55)
Age at treatment, mean (SD) years	67.72 (9.69)
Mean duration of treatment (SD)	64.24 (12.14)
Smoking status	*n* (%)
Current smoker	117(35.8)
Former smoker	21 (6.4)
Nonsmoker	189 (57.8)
Immunocompromised	*n* (%)
Yes	12 (3.7)
No	315 (96.3)
CFT location	*n* (%)
Face/ears	271 (82.9)
Scalp	56 (17.1)
Had pre-treatment in-field cancer	*n* (%)
Yes	75 (22.9)
No	252 (77.1)
Had post-treatment in-field cancer	*n* (%)
Yes	8 (2.4)
No	319 (97.6)
Had pre-treatment out-of-field cancer	*n* (%)
Yes	79 (24.2)
No	248 (75.8)
Had post-treatment out-of- field cancer	*n* (%)
Yes	27 (8.3)
No	300 (91.7)

CFT, Chemoprevention Field Therapy; SD, standard deviation.

where those who completed the treatment faster than recommended in the treatment guidelines (ie, <42 days) were excluded from analyses such that the sample consisted of only those who completed the chemoprevention treatment in 42 to 76 days.

RESULTS

In this sample of 849 patients, 327 met the inclusion criteria of having completed the field chemoprevention treatment of 30 applications within a 30 to 76 day window and having data available in the database for one year prior to initiation of chemoprevention treatment and one year after completion of chemoprevention treatment. Sample characteristics are described (Table 1).

Among the patients who met inclusion criteria, 75 had in-field cancer the year prior to treatment, and 8 had in-field cancer the year after treatment. These patients had lower odds of having in-field cancer in the year after treatment than the year prior (OR = 0.06, 95% CI [0.02, 0.15]). Similar associations were noted when examining SCC and BCC separately (OR = 0.05, 95% CI [0.01, 0.35]; OR = 0.09, 95% CI [0.04, 0.22], respectively). Patients were also at lower odds of having an out-of-field cancer post-treatment than they were pre-treatment (overall: OR = 0.25; 95% CI [0.14, 0.42]; SCC: OR = 0.29, 95% CI [0.15, 0.54]; BCC: OR = 0.15, 95% CI [0.06, 0.38]; melanoma: OR = 0.50, 95% CI [0.09, 2.73]; Table 2). Additionally, patients had fewer cryotherapy sessions in the year post-treatment (mean=1.5, SD=1.21) than the year prior (mean=2.3, SD=0.99) (t=11.68, P<0.001; Table 3).

In the analyses stratified by smoking status, similar associations were noted though non-smokers seemed to derive greater benefits from chemoprevention than smokers. Among both

TABLE 2.

Associations Between Treatment and Presence of Skin Cancer			
	Patients with a lesion in the year prior to treatment	Patients with a lesion in the year after treatment	OR (95% CI)[a]
Full Sample (n=327)			
In-field overall	75	8	0.06 (95% CI: 0.02, 0.15)
In-field SCC	21	1	0.05 (95% CI: 0.01, 0.35)
In-field BCC	58	7	0.09 (95% CI: 0.04, 0.22)
Out-of-field overall	79	27	0.25 (95% CI: 0.14, 0.42)
Out-of-field SCC	47	17	0.29 (95% CI: 0.15, 0.54)
Out-of-field BCC	37	8	0.15 (95% CI: 0.06, 0.38)
Out-of-field melanoma	4	2	0.50 (95% CI: 0.09, 2.73)
Non-Smokers (n=189)[b]			
In-field overall, non-smoker	49	2	0.02 (95% CI: 0.003, 0.15)
Out-of-field overall, non-smoker	40	14	0.26 (95% CI: 0.12, 0.53)
Current Smokers (n=117)[b]			
In-field overall, current smoker	22	6	0.16 (95% CI: 0.05, 0.53)
Out-of-field overall, current smoker	30	12	0.31 (95% CI: 0.14, 0.68)

[a]Odds ratios were derived from conditional logistic regressions. [b]Twenty-one participants were former smokers and were thus not included in these subset analyses.
BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

TABLE 3.

Cryotherapy Sessions Before and After Treatment				
	Sessions-Pre-Treatment*	Sessions-Post-Treatment*	t-statistic	*P*-value
Non-Stratified Analysis				
Cryotherapy sessions	2.3 (0.99)	1.47 (1.21)	11.68	<.001
Stratified Analysis, Smoking Status				
Cryotherapy sessions, non-smoker	2.3 (0.97)	1.4 (1.24)	9.2	<.001
Cryotherapy sessions, current smoker	2.4 (0.97)	1.5 (1.19)	6.9	<.001

*Mean (SD)

smokers and non-smokers, odds of cancer occurrence were lower in the year after treatment than the year before treatment for both in-field (smokers: OR=0.16, 95% CI [0.05, 0.53]; non-smokers: OR=0.02, 95% CI: [0.003, 0.16]) and out-of-field cancers (smokers: OR=0.31, 95% CI [0.14, 0.68]; non-smokers: OR=0.26, 95% CI: [0.12, 0.53]; Table 2). Similarly, the mean number of cryotherapy sessions was lower in the year after treatment (smokers: mean=1.5, SD=1.19; non-smokers: mean=1.4, SD=1.24) than the year before treatment (smokers: mean=2.4, SD=0.97; non-smokers: mean=2.3, SD=0.97) for both smokers and non-smokers (Table 3). Sensitivity analyses, which excluded those with a treatment duration of fewer than 42 days, yielded results that were not different from those in the primary analyses.

DISCUSSION

In this study, we included data from 327 patients who employed IMI/5-FU/TRET in a field therapy regimen over the face/ears and scalp and found a dramatic decrease in the odds of KCs in the treatment location (face/ears or scalp) in the one-year period after field treatment when compared with that one year before field treatment. There were also lower odds of KCs in the non-treated areas after the field treatment on the face/ears or scalp, as well as a reduction in the number of cryotherapy sessions performed for AKs in the treatment areas for a period of one year compared with the year before treatment.

Field therapy with IMI/5-FU/TRET can be an effective tool for providing chemoprevention of KCs for at least one year. Previous studies have shown that treatment side effects, including cutaneous irritation and pain, may be limiting factors in completing a treatment course.[27,28] However, these deleterious effects can potentially be mitigated by using intermittent dosing and lower doses, which may be possible when using combination chemoprevention, as opposed to standalone treatments.[27,28] Moreover, educating patients about these potential side effects beforehand,[29] as well as describing how this option may help them avoid surgery, may help increase patient adherence.

In previous studies, extending the 30 applications of local combination treatment beyond 76 days was found to reduce the efficacy of KC treatment.[30] Therefore, this study used 76 days as the upper limit for inclusion. We have already seen that by allowing the patient to determine their pausing of application, change in frequency of application, and use of clobetasol, a high percentage of patients were able to complete the overall treatment regimen (30 applications) for chemoprevention. Although the patients were given similar instructions, a total of 27 patients completed the 30 treatments before day 42, while 300 patients completed the 30 treatments within 42 to 76 days.

Notably, while the IMI/5-FU/TRET regimen was effective in preventing KCs in-field, it also prevented these lesions and melanomas in out-of-field treatment areas. The direct effects are likely due to imiquimod's ability to bind toll-like receptors on white blood cells and activate apoptosis in tumor cells. Indirectly, imiquimod also has activity against tumor cells by inducing the release of IL-12, TNF-alpha, and IFN-gamma. Through the resulting cell-mediated immune response, imiquimod can target AKs both in-field and out-of-field, thereby preventing their progression to KCs.[31,32]

In addition to using immunomodulators like imiquimod to treat AKs, previous studies have shown that, through vaccines, it may be possible to train a person's immune system to prevent the development of KCs. For example, a case series found that, after 3 doses of the quadrivalent HPV vaccine, there was a reduction in the number of KCs that these patients developed.[33] Another viable alternative method to treat AKs, and thus help prevent the development of KCs, is niacinamide, which has potent photoprotective and anti-inflammatory effects.[34] To maximize patient adherence, the choice of regimen should be individualized to the patient's condition, as well as their needs and treatment goals.

In our data analysis, it seems that non-smokers derived greater benefits from IMI/5-FU/TRET chemoprevention than smokers. This interesting observation suggests that smoking has deleterious effects on immune responses with chemoprevention. This is consistent with a study that demonstrated smoking had an unfavorable outcome by decreasing the protective value of immune infiltration in melanomas.[35] Previous studies with niacinamide chemoprevention showed no differences between smokers and non-smokers.[36] Most studies with KC chemoprevention did not look at its association with smoking.[7,9,10,13,14,16-18] In terms of incidence, previous studies show that current smokers had lower risks of melanomas[37] and BCCs, but higher risks of SCCs.[38]

Although quantifying the number of AKs treated with cryotherapy was not possible, there was a statistically reduced number of cryotherapy sessions in the year after the chemoprevention treatment compared with that of the year prior to the chemoprevention regimen. This finding may imply that fewer AKs needed to be treated with the IMI/5-FU/TRET regimen.

This study had notable limitations. The retrospective nature of the study may have introduced bias into the analyses and prevented us from being able to assess causality. Given that the KCs observed in the year prior to treatment may have developed over several years prior to diagnosis, whereas KCs in the year after treatment could only have developed during the one year of observation, it is likely that the number of lesions observed in the year prior to treatment represents more than one year of KC growth. Therefore, although the present study is suggestive of combination therapy being effective for protection against KCs, prospective studies or randomized controlled trials will be necessary to better understand the effects of IMI/5-FU/TRET therapy.

DISCLOSURES

The authors have no conflicts of interest to declare.

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