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A Non-Surgical and Cost-Effective Treatment Approach Employing Topical Imiquimod, 5-Fluorouracil, and Tretinoin for Primary Non-Melanoma Skin Cancers

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ABSTRACT

Background: Minimally invasive alternative approaches to treat non-melanoma skin cancers remain limited and unproven.

Objective: We aim to assess the efficacy of varying combinations of anti-tumor agents—imiquimod 5% cream, 5-fluorouracil 2% solution, and tretinoin 0.1% cream—with brief cryotherapy in treating non-melanoma skin cancers.

Methods: This retrospective study included 690 cases of non-melanoma skin cancers in 480 patients who received a diagnosis of a basal cell carcinoma or squamous cell carcinoma during a ten-year period. During treatment period, patients applied 30 applications of one of three combinations (imiquimod/tretinoin, 5-fluorouracil/tretinoin, or imiquimod/5-fluorouracil/tretinoin) and had cryotherapy every 2 weeks. Each patient had a clinical examination at least three years post-treatment or documented treatment failure. Clearance was defined by a lack of persistence or recurrence for 3 years following the completion of treatment. The likelihood of lesion clearance was evaluated using multivariable logistic regression analysis.

Results: A total of 186 cases (97; basal cell carcinoma and 89; squamous cell carcinoma) in 133 patients [37% women and 63% men; median (interquartile range) age, 77 (69, 83) years] met the inclusion criteria. Multivariable logistic regression analysis adjusting for clinical and lesion variables demonstrated that, relative to the imiquimod/5-fluorouracil/tretinoin treatment approach, imiquimod/tretinoin (odds ratio, 0.05; 95% confidence interval, 0.00-0.99) and 5-fluorouracil/tretinoin (0.02; 0.00–0.45) were associated with lower likelihoods of lesion clearance. Likewise, morpheaform basal cell carcinoma had a lower probability of clearance (0.05; 0.00–0.72).

Conclusions: The combination of imiquimod/5-fluorouracil/tretinoin with cryotherapy had high clearance rates and was the most effective treatment regimen.

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INTRODUCTION

Non-melanoma skin cancers (NMSCs), predominately comprised of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most common malignancies, affecting around 5.4 million people a year in the United States (US).[1,2] The incidence of NMSCs continues to rise with estimates suggesting over 2 million and 1 million new cases of BCC and SCC, respectively, in the US each year.[3-5] From 2000 to 2010, the BCC incidence rose 145% and SCC incidence rose 263%.[4,6] Similar, but less dramatic, rises were seen worldwide.[7]

The annual expenditure to treat NMSCs is increasing more rapidly than those to treat any other cancers, with average costs approaching $4.8 billion per year in the US. This number highlights the considerable health and economic burden of these malignancies.[8] Surgical excision including Mohs micrographic surgery (MMS) remain the standard for the treatment of NMSCs.[9,10] However, surgical approaches are associated with direct high financial costs, indirect costs such as lost work productivity, complications such as infections, and potentially poor cosmetic outcomes. Other treatment options

include cryotherapy, curettage and electrodesiccation, topical therapies, radiation therapy (RT), laser treatment, intralesional interferon-alpha, electrochemotherapy, intralesional 5-FU, intralesional methotrexate, intralesional bleomycin, combined systemic and intratumoral human papillomavirus vaccine, and photodynamic therapy.[9,11-16] These treatments, however, are often not approved by the US Food and Drug Administration for the treatment of skin cancers, and their clearance rates are often limited and unknown.

Performing a retrospective review, we sought to evaluate the effectiveness and tolerability of varying combinations of topical therapy [imiquimod 5% cream (IMI), 5-fluorouracil 2% solution (5-FU), and tretinoin 0.1% cream (TRET)] and cryotherapy used to treat NMSCs. The effectiveness of the differing combinations of topicals was determined by their rates of tumor clearance over a three-year post-treatment period.

MATERIALS AND METHODS

Study Design

Data originated from the charts of patients in a dermatology practice seen from September 1, 2009 to December 31, 2019. This study was approved by the University of Miami's Institutional Review Board.

We identified 480 patients with 690 cases of NMSC who had a diagnosis of BCC or SCC that were treated with topical combinations. BCCs were classified into superficial (sBCC), nodular (nBCC), and morpheaform (mBCC). SCCs were subdivided into invasive (ISCC) and in situ (SCCIS).[11,17] Patient characteristics, including age, gender, immunosuppression, and smoking history, were noted. Additional data collected were the date of the diagnostic biopsy, size of the tumor (pre-treatment), treatment regimen, start and completion dates of therapy, the outcome of treatment, follow-up duration, side effects, presence of post-treatment cosmetic acceptability, and clinical images.

To be eligible for study inclusion, the patients must have had completed exactly 30 treatments of a combination of topical therapy with lesional cryotherapy, occurring every two weeks (n=265 cases excluded) within 76 days after starting the first treatment (n=15 excluded). Also, patients needed to have a clinical examination three years post-treatment or a documented treatment failure, which was defined as persistence or recurrence of the tumor within three years (n=224 excluded).

Treatments

Patients with NMSC who declined surgical and other treatment options were prescribed one of three topical combination regimens: IMI/TRET, 5-FU/TRET, or IMI/5-FU/TRET. Each treatment regimen was determined by the patient's insurance or ability to afford each of the medications. Patients were instructed to apply the combination of topical medications to the tumor 5 days a week for 6 weeks. Specified amounts of the medications included 1/5 of a pea-sized amount ofTRET and/or 1/5 of a packet of IMI and/or 1 drop of 5-FU. The medications were combined on a bandage that was placed on the lesion overnight. Cryotherapy was performed for 1 second with 1-2 mm margins on the lesion before initiating topical treatment and at each visit.

All patients experienced some amount of local skin reactions that included erythema, scaling, burning, erosion, and pain. If any adverse effects caused significant discomfort, patients were advised to stop the applications until the symptoms subsided and to reduce the frequency of applications to 2 or 3 days/week resulting in an extended treatment period.

Patients were evaluated at the clinic every 2 weeks during the treatment course and were treated with brief cryotherapy. Clinical images were taken before a biopsy, before initiating treatment, and at every visit. Some patients opted to use a store-and-forward application to decrease visit-associated costs. The application allowed patients to answer questions about their adverse events, upload photos of their treatment sites, and receive prescribing information. Following treatment, patients and their treatment sites were periodically monitored for a minimum of 3 years. If tumor persistence or recurrence was suspected clinically after completion of therapy, the lesion was re-biopsied.

Statistical Analysis

The primary outcome, clearance, was defined by a lack of clinical evidence of persistence or recurrence following the completion of treatment to the follow-up examination of at least 3 years. Treatment duration was calculated from the first application of therapy to the last of the 30 applications. The follow-up period was determined by calculating the days from the final treatment to the last visit when the lesion was evaluated. Chi-square tests were used to compare clearance rates of treatment groups to determine if there were significant variability in the effectiveness of the three combinations (IMI/TRET; 5-FU/TRET; IMI/5-FU/TRET) for each cancer subtype. Multivariate logistic regression was used to model the likelihood of clearance among the full study cohort. The regression adjusted for the treatment group, lesion subtype, location, gender, smoking status, immunosuppression status, and quadratic transformation of age. Akaike information criterion (AIC) minimization was used to compare differences in model fit when variables were evaluated for inclusion as covariates within the model. For descriptive statistics, bivariate differences between treatment groups were assessed using chi-squared-tests and Kruskal-Wallis tests, as appropriate. Statistical analysis was performed using Stata version 16.1 (Stata Corp, College Station, TX).

RESULTS

Patient and clinical characteristics of 186 cases of NMSC (97

TABLE 1.

Patient Characteristics by Skin Cancer and Treatment Group

Variable	Overall (N = 186)†	Treatment Group						
		BCC (N = 97)			SCC (N = 89)			P Value (BCC; SCC)
		IMI/TRET (n = 51)	5-FU/TRET (n = 13)	IMI/5-FU/TRET (n = 33)	IMI/TRET (n = 39)	5-FU/TRET (n = 15)	IMI/5-FU/TRET (n = 35)	
Age, median (interquartile range)	77 (69, 83)	72 (61, 80)	82 (75, 85)	74 (65, 79)	79 (71, 83)	81 (71, 90)	79 (73, 83)	.04; .68
Lesion Size (mm), median (interquartile range)	6 (3, 10)	4 (3, 10)	8 (3, 10)	4 (3, 8)	7 (3, 10)	8 (4, 10)	7 (4, 10)	.59; .77
Gender								
Woman	68 (37%)	20 (39%)	2 (15%)	7 (21%)	17 (44%)	5 (33%)	17 (49%)	.10; .61
Man	118 (63%)	31 (61%)	11 (85%)	26 (79%)	22 (56%)	10 (67%)	18 (51%)	
Smoking History								
No	140 (75%)	38 (75%)	9 (69%)	26 (79%)	28 (72%)	12 (80%)	27 (77%)	.78; .78
Yes	46 (25%)	13 (25%)	4 (31%)	7 (21%)	11 (28%)	3 (20%)	8 (23%)	
Immunosuppressed								
No	177 (95%)	51 (100%)	13 (100%)	32 (97%)	39 (100%)	11 (73%)	31 (89%)	.38; .007
Yes	9 (5%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	4 (27%)	4 (11%)	
Lesion Subtype								
Superficial BCC	14 (8%)	8 (16%)	2 (15%)	4 (12%)	--	--	--	.66; .27
Nodular BCC	72 (39%)	38 (75%)	8 (62%)	26 (79%)	--	--	--	
Morpheaform BCC	11 (6%)	5 (10%)	3 (23%)	3 (9%)	--	--	--	
SCC In Situ	38 (20%)	--	--	--	26 (67%)	7 (47%)	18 (51%)	
Invasive SCC	51 (27%)	--	--	--	13 (33%)	8 (53%)	17 (49%)	
Lesion Location								
Head/Neck	92 (49%)	32 (63%)	7 (54%)	23 (70%)	10 (26%)	3 (20%)	17 (49%)	.92; .15
Trunk	24 (13%)	8 (16%)	2 (15%)	5 (15%)	6 (15%)	1 (7%)	2 (6%)	
Upper Extremity	48 (26%)	7 (14%)	3 (23%)	4 (12%)	16 (41%)	9 (60%)	9 (26%)	
Lower Extremity	22 (12%)	4 (8%)	1 (8%)	1 (3%)	7 (18%)	2 (13%)	7 (20%)	
Treatment Period > 42 days‡								
No	59 (32%)	17 (33%)	6 (46%)	6 (18%)	12 (31%)	9 (60%)	9 (26%)	.13; .06
Yes	127 (68%)	34 (67%)	7 (54%)	27 (82%)	27 (69%)	6 (40%)	26 (74%)	

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma; IMI, Imiquimod 5% cream; 5-FU, 5-Fluorouracil 2% solution; TRET, Tretinoin 0.1% cream.
†In 133 patients. ‡Completed 30 treatments of topical therapy between 42 and 76 days.

TABLE 2.

Clearance Rates by Topical Therapy, Stratified by Type and Subtype of Skin Cancer†

Treatment Group	BCC				SCC			Overall
	Superficial	Nodular**	Morpheaform	Total	In Situ*	Invasive	Total	
IMI/TRET	100% (8/8)	97% (37/38)	60% (3/5)	94% (48/51)	92% (12/13)	96% (25/26)	95% (37/39)	94% (85/90)
5-FU/TRET	100% (2/2)	75% (6/8)	100% (3/3)	85% (11/13)	63% (5/8)	86% (6/7)	73% (11/15)	79% (22/28)
IMI/5-FU/TRET	100% (4/4)	100% (26/26)	67% (2/3)	97% (32/33)	100% (17/17)	100% (18/18)	100% (35/35)	99% (67/68)
Overall	100% (14/14)	96% (69/72)	73% (8/11)	94% (91/97)	89% (34/38)	96% (49/51)	93% (83/89)	94% (174/186)

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma; IMI, imiquimod 5% cream; 5-FU, 5-fluorouracil 2% solution; TRET, tretinoin 0.1% cream.
†Clearance rates of each treatment group, stratified by skin cancer subtype, were compared using chi-square tests. *$P \leq .05$. **$P \leq .01$.

TABLE 3.

Treatment Failures								
Case	Age	Gender	Size (mm)	Subtypes	Location	Topical Therapy	Smoking History‡	Immunosuppressed
1	82	M	3	nBCC	Head/Neck	5-FU/TRET	No	No
2	74	M	20	nBCC	Head/Neck	5-FU/TRET	No	No
3	80	M	10	nBCC	Lower Extremity	IMI/TRET	Yes	No
4	87	M	10	mBCC	Head/Neck	IMI/TRET	Yes	No
5	81	M	12	mBCC	Head/Neck	IMI/TRET	Yes	No
6	75	M	6	mBCC	Head/Neck	IMI/5-FU/TRET	No	No
7†	81	M	10	SCCIS	Upper Extremity	5-FU/TRET	No	Yes
8†	81	M	10	SCCIS	Upper Extremity	5-FU/TRET	No	Yes
9†	81	M	10	SCCIS	Upper Extremity	5-FU/TRET	No	Yes
10	85	M	2	SCCIS	Head/Neck	IMI/TRET	No	No
11	88	M	10	ISCC	Upper Extremity	IMI/TRET	No	No
12	67	W	10	ISCC	Lower Extremity	5-FU/TRET	No	No

Abbreviations: nBCC, nodular basal cell carcinoma; mBCC, morpheaform basal cell carcinoma; SCCIS, squamous cell carcinoma in situ; ISCC, invasive squamous cell carcinoma; IMI, imiquimod 5% cream; 5-FU, 5-fluorouracil 2% solution; TRET, tretinoin 0.1% cream.
†Cases were from the same patient. ‡Greater than 10 pack years.

BCC; 89 SCC) are presented in Table 1 [in 133 patients; 37% women and 63% men; median (interquartile range; IQR) age, 77 (69, 83) years]. Three-quarters of the cases (140/186) involved patients who were nonsmokers, and 5% of cases (9/186) involved immunosuppressed patients. The median (IQR) size of all lesions treated was 6 (3,10) mm. The majority of NMSCs were nBCCs (n=72, 39%). ISCCs (n=51, 27%), SCCISs (n=38, 20%), sBCCs (n=14, 8%), and mBCCs (n=11, 6%) followed accordingly (Table 1). Significant variability in the effectiveness of the three topical therapies was found for nBCC ($P \leq 0.01$) and SCCIS ($P \leq 0.05$) (Table 2).

All 97 cases of BCC were treated with either IMI/TRET (n=51), 5-FU/TRET (n=13), or IMI/5-FU/TRET (n=33) (Table 1). The total clearance rate of all three treatment groups for BCC was 94%. The clearance rates were as follows for each treatment group: IMI/TRET, 94%; 5-FU/TRET, 85%; and IMI/5-FU/TRET, 97% (Table 2). A total of 6 BCC (nBCC, 3; mBCC, 3) recurrences were identified among the 97 cases. Five of the recurrences were found on the head/neck area, and 1 was found on the lower extremity. The 6 recurrent cases involved men greater than 70 years of age, of which 3 had a history of smoking >10 pack years. Three of the recurrences occurred in the IMI/TRET group, 2 in the 5-FU/TRET group, and 1 in the IMI/5-FU/TRET group (Table 3).

A total of 89 cases of SCC were treated with one of the following combinations IMI/TRET (n=39), 5-FU/TRET (n=15), or IMI/5-FU/TRET (n=35) (Table 1). A clearance rate of 93% was determined for all the SCC groups. The clearance rates were as follows for each treatment group: IMI/TRET, 95%; 5-FU/TRET, 73%; and IMI/5-FU/TRET, 100% (Table 2). A total of 6 SCC recurrences were found among the 89 cases. Three recurrences occurred in an immunosuppressed elderly man treated with 5-FU/TRET. Two recurrences were in men treated with IMI/TRET, and one was in a woman treated with 5-FU/TRET (Table 3).

Multivariate analysis demonstrated variability with the effectiveness of the treatment combinations with the likelihood of NMSC clearance (Table 4). Patients in certain groups were less likely to have NMSC clearance. Relative to IMI/5-FU/TRET patients, both IMI/TRET (odds ratio [OR], 0.05; 95% CI, 0.00–0.99) and 5-FU/TRET (OR, 0.02; 95% CI, 0.00–0.45) had lower odds of clearance, adjusting for other factors. Holding other variables constant at their means, the clearance rate with 5-FU/TRET was 95.0%, IMI/TRET was 97.0%, and IMI/TRET/5-FU was 99.9%. Relative to being diagnosed with a nBCC, having a mBCC resulted in a lower chance for clearance (OR, 0.05; 95% CI, 0.00–0.72); none of the other lesion subtypes were significantly different from nBCC. The rest of the factors adjusted for in the regression were not found to be associated with the likelihood of clearance. However, the area under the receiver operating characteristic curve was 0.91, indicating that the model has a very high degree of predictive accuracy.

With each case, every patient reported a cosmetically acceptable final appearance of their treated site (Figure 1). There was no significant difference in lesion size between cases that failed treatment and cases that succeeded. Most patients in the study spread out their 30-application treatment course beyond the minimum treatment period (Table 1). The percentage of patients that extended their treatment period was 68% (127/186) overall. Extending the treatment period up to 76-days was not found to reduce treatment efficacy, and the categorical variable was excluded from the model after conducting AIC minimization. In the IMI/5-FU/TRET treatment group, which had an overall clearance rate of 99% (Table 2), most patients (84%, BCCs; 74%,

TABLE 4.

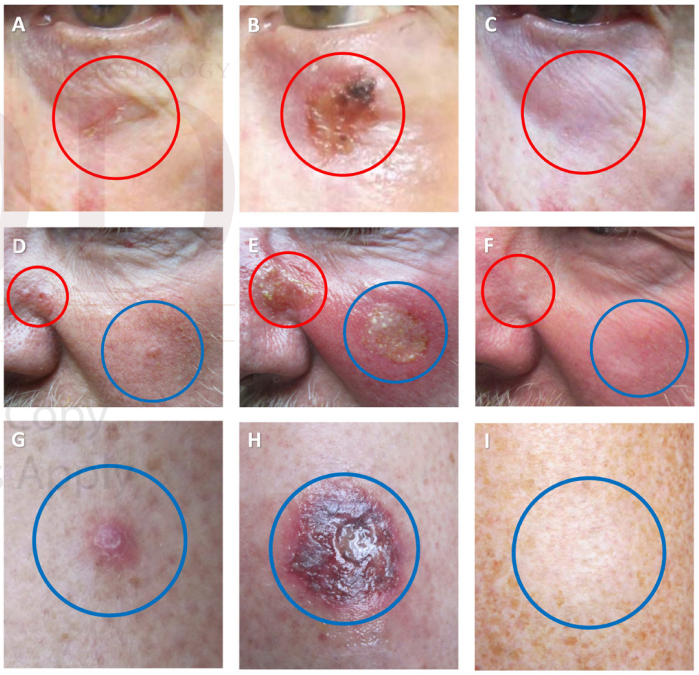
Multivariate Analysis of Factors Associated With Likelihood of Having Non-melanoma Skin Cancer Clearance†

Variable	Odds Ratio (95% Confidence Interval)	*P* Value
Treatment Group		
IMI/TRET	0.05 (0.00,0.99)	.05
5-FU/TRET	0.02 (0.00,0.45)	.01
IMI/5-FU/TRET	1 [Reference]	--
Lesion Subtype		
BCC		
Superficial‡	1 (1.00,1.00)	--
Nodular	1 [Reference]	--
Morpheaform	0.05 (0.00,0.72)	.03
SCC		
In Situ	0.93 (0.07,12.71)	.96
Invasive	0.60 (0.06,6.41)	.67
Lesion Location		
Head/Neck	1 [Reference]	--
Trunk§	1 (1.00,1.00)	--
Upper Extremity	3.31 (0.32,34.44)	.32
Lower Extremity	0.89 (0.06,12.72)	.93
Gender		
W	1 [Reference]	--
M	0.12 (0.01,2.27)	.16
Smoking History		
No	1 [Reference]	--
Yes	6.91 (0.67,70.91)	.10
Immunosuppressed		
No	1 [Reference]	--
Yes	0.08 (0.00,2.64)	.16
Age	0.18 (0.02,1.76)	.14
Age^2	1.01 (1.00,1.03)	.14
Size (mm)	0.87 (0.74,1.03)	.12

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma; IMI, imiquimod 5% cream; 5-FU, 5-fluorouracil 2% solution; TRET, tretinoin 0.1% cream.
†Treatment period greater than 42 days was excluded from the multivariable model after Akaike information criterion minimization. ‡14 cases with superficial BCC were omitted because all had clearance. §19 cases with a trunk location were omitted because all had clearance.

SCCs) extended their treatment period (Table 1). The 5-FU/TRET and IMI/TRET treatment groups had lower combined clearance rates of 79% and 94%, respectively, despite having a lower proportion of patients with extended treatment periods (Table 2). In the 5-FU/TRET group, 54% of the patients with BCCs and 40% of the patients with SCCs extended their treatment period. In the IMI/TRET group, 67% of the patients with BCCs and 69% of the patients with SCCs extended their treatment period (Table 1).

FIGURE 1. Clinical images of NMSCs on the face before, during, and after treatments with combination topical therapies. (A) BCC (morpheaform; red circle) on the left superior cheek at the infraorbital margin. (B) BCC (morpheaform) treated with IMI/5-FU/TRET after 30 applications (red circle), demonstrating erythema, scaling, and crusting. (C) Post-treatment area (red circle) 3 years after the last treatment application with good cosmetic outcome. (D) A BCC (nodular, red circle) on the left nasofacial sulcus and a SCC (invasive, blue circle) on the left malar cheek area. (E) A BCC (red circle) and an SCC (blue circle) treated after 30 applications of IMI/5-FU/TRET, demonstrating erythema, erosion, and eczematous-like reaction. (F) Post-treatment areas after 3 years, demonstrating no clinical signs of recurrence and good cosmesis. (G) SCC (invasive, blue circle) on the right lower extremity. (H) SCC treated with IMI/TRET after 20 applications showing purpura and ulceration. (I) Post-treatment area after 3 years demonstrating acceptable cosmetic outcome.



Abbreviations: NMSCs, non-melanoma skin cancers; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; IMI, imiquimod 5% cream; 5-FU, 5-fluorouracil 2% solution; TRET, tretinoin 0.1% cream.

DISCUSSION

The incidence of skin cancers is on the rise, with a correlated increased economic burden to society.[18] Furthermore, surgery is the gold standard for the treatment of NMSCs, but patients can also incur significant costs with these procedures.[19,20] Although all the patients with NMSCs were encouraged to undergo standard of care surgical treatments for their NMSCs, many of these patients due to insurance issues or lack of insurance could not afford such treatments and therefore declined such procedures. In addition, some patients, for various reasons, were totally unwilling to have a surgical procedure.

Our therapies involving office visits, intermittent cryotherapy, and combination of topicals [*99213*6*($79.43*6=$476.58); *17000*6*($70.79*6=$424.74); 5-fluorouracil 2% solution (10 ml) – $29.25; imiquimod 5% (30 pack) – $28.18; tretinoin 0.1% cream (20 gm) – $35.30] would cost minimally around $994.05. Also, the implementation of a store-and-forward technology was employed at the behest of the patients to reduce visit costs from $476.58 to $50.00.[21] Typical treatment for a facial NMSC with Mohs surgery (2 stages) and flap reconstruction in a surgery center would cost around 3-4 times ($3131.58) as much. Radiation therapy, which includes superficial or orthovoltage RT, electron beam therapy, and high dose-rate brachytherapy, requires many fractionated treatments (up to 17 fractionations).[22] These treatment costs are up to 13–14 times greater than the combination modalities. Interferon-alpha-2b injections[23,24] can cost up to 2–3 times more than our treatment modalities. Moreover, intralesional interferon requires weekly lab monitoring.[25] Intralesional methotrexate (1–5 injections) is less costly, but intralesional methotrexate has been only used to treat keratoacanthomas[26] Intralesional bleomycin and fluorouracil also have costs that are similar to our treatment modality and may require weekly blood monitoring.[27] These costs were derived from Medicare rates (California, Area 72, 2019), and medication costs were derived from GoodRx.

Imiquimod and 5-fluorouracil are approved by the FDA to treat actinic keratoses (AKs) and sBCC.[28] Imiquimod, 5-fluorouracil, and retinoids all possess anti-tumor properties. Imiquimod is a topical immune response modifier that binds to toll-like receptors on phagocytes and activates both the innate and adaptive immunity.[29] It has been shown to recruit specific populations of effector T-cells that infiltrate SCCs, release cytotoxic cytokines, and inhibit anti-inflammatory signals, ultimately leading to tumor regression.[30] 5-fluorouracil is an antineoplastic agent that induces a cytotoxic effect by forming metabolites that interfere with the synthesis and function of RNA and DNA.[31] Retinoids can downregulate keratinocyte differentiation and proliferation and may lead to necrosis and apoptosis of atypical lesions.[32] Retinoids are also thought to enhance penetration of other topically applied medications through their ability to reduce epidermal hyperkeratinization.[33] Most studies show no difference in the primary outcomes for new BCCs or ISCCs with tretinoin 0.1% cream.[1,25]

It has been hypothesized that combining these topical medications may be more effective than monotherapy through synergism. Imiquimod induces the production of several inflammatory cytokines, such as IFN and IL-12, that upregulate the enzyme thymidine phosphorylase, which is responsible for converting 5-fluorouracil to its active metabolite, therefore enhancing its therapeutic effects.[33,34] Our combination of IMI/5-FU/TRET resulted in a high overall clearance rate, which is consistent with this purported synergism.

Success rates of 87-88% for sBCC and 75% for nBCC have been reported for imiquimod 5% treatments.[35] Although excision has higher clearance rates than topical imiquimod treatments for BCC, the cosmetic outcome with imiquimod treatments was found to be significantly better in one study.[35] In another study, topical 5-fluorouracil 5% and imiquimod 5% were found to have similar clearance rates and cosmetic outcomes for BCCs.[36] The addition of TRET and cryotherapy to IMI may have increased the clearance rate for BCCs in comparison to those of imiquimod monotherapy.[35]

Imiquimod 5% and 5-fluorouracil 5% have also been successfully used off-label as monotherapy and in a mixture for the treatment of SCCIS and ISCC.[28,34,37-42] Clearance rates of 70%-100% were reported in several studies of SCCIS or ISCC.[25,39-41] Lower clearance rates were observed when topicals were used as monotherapy, although monotherapy with imiquimod seems to be more effective than monotherapy with 5-fluorouracil for SCCs.[25,39-41] These results are consistent with our study, in which we observed lower clinical clearance rates for the IMI/TRET group and the 5-FU/TRET group. Our study demonstrated a clearance rate of 100% in 35 cases of SCC treated with IMI/5-FU/TRET and cryotherapy (Tables 1,2). The only other comparable study to this treatment showed that a combination of imiquimod 5% and 5-fluorouracil 5% had a 100% clearance rate of SCCIS in four patients.[34]

The triple combination of IMI/5-FU/TRET was the most effective treatment regimen, with little to no NMSC recurrence and the highest adjusted probability of tumor clearance (99.9%) among the three therapies (Tables 1,2). IMI/TRET was less effective, with clearance rates approaching 94% for BCCs and 95% for SCCs and a lower likelihood of clearance (97.6%). The 5-FU/TRET combination was the least effective in the treatment of BCCs (85%) and SCCs (73%) (Table 2) with the lowest likelihood of clearance (95%). These lower observed clearance rates were consistent with previous studies involving monotherapy with imiquimod or 5-fluorouracil over much more prolonged periods.[28,34,35,37-42] Although IMI/5-FU/TRET was effective in the treatment of mBCCs (Table 2), multivariate analysis demonstrates this high-risk morpheaform subtype was associated with a lower likelihood of clearance relative to the other subtypes (Tables 4). Considering this, Mohs surgery should still be given the greatest consideration in the treatment of high-risk mBCC.

Both topical 5-fluorouracil and imiquimod are associated with side effects of inflammatory reactions.[25,37-39] These adverse effects prevented many patients from completing their treatment protocols, which, in some studies lasted as long as 16 weeks (224 applications).[42] As such, our treatment protocol was limited to 30 applications so that patients could reasonably complete the process with limited side effects. Although most of the patients

did extend the treatment period of 30 applications beyond the 42-day minimum treatment period, no patient who extended their treatments beyond 42 days was unable to complete a total of 30 applications. From our previous experience, patients did not seem to be able to tolerate or complete a greater number of applications of the combination. Moreover, poorer clearance rates were seen when extending the 30 treatment applications beyond 76 days (data not shown).

Cryotherapy as monotherapy has been shown to have varying recurrence rates for SCCIS from 0% to 50%.[38,43] For BCCs, the recurrence rate with cryotherapy ranged from 5% to 39%.[44,45] Intralesional cryotherapy to treat SCCs has been described with 2 freeze-thaw cycles of 30 to 60 seconds.[46] Also, cryotherapy with 20 seconds of freeze, 60 seconds of thaw with 2 cycles had no difference in recurrence rates compared with standard surgical excision for sBCCs or nBCCs.[47] The drawbacks of the prolonged cryotherapy with multiple freeze-thaw cycles were unacceptable cosmetic outcomes and persistent pain.[38,45] We did not employ prolonged cryotherapy because of the increased morbidity. Instead, cryotherapy was administered briefly to increase the local penetration of topical medications. Moreover, cryotherapy is thought to release tumor antigens, stimulating an immune response that can be enhanced by the immunostimulant effects of anti-tumor topical medications.[48,49]

This was an observational study with non-random assignment of patients to determine the efficacy of non-invasive therapies to treat NMSCs. Although all covariates available in the charts were controlled for in the multivariable model, it is still possible that the findings are a result of an unmeasured confounder and not a true association between the likelihood of clearance and treatment groups. A potential unmeasured confounder could be the innate immune response of an individual against NMSCs. Using subtype of skin cancer as an interaction term for the type of the topical therapy may be a preferred modeling approach, but the sample sizes within the interacted groups were relatively small and resulted in too many perfect predictions. In light of the new need for social distancing, further studies using these combinations for the treatment of NMSCs without cryotherapy and with telehealth are needed.

CONCLUSION

We present evidence of a therapy for low-risk NMSCs that combines imiquimod, 5-fluorouracil, and tretinoin with brief cryotherapy that is highly effective, cost-efficient, minimally invasive, less irritating, and favorable for a good cosmetic outcome. Considering the rapidly increasing costs of treating both BCCs and SCCs, this approach to treating NMSCs may become more warranted.

DISCLOSURES

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