COMBINATION THERAPY WITH SHORT CONTACT TOPICAL CALCIPOTRIENE FOAM AND FLUOROURACIL FOLLOWING CRYOTHERAPY FOR ACTINIC KERATOSIS

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INTRODUCTION

- Actinic keratoses (AKs) are lesions characterized by a proliferation of dysplastic keratinocytes that occur on photoaged skin as a result of ultraviolet radiation. They have malignant potential and are recognized precursors to squamous cell carcinoma (SCC).[1,2]
- The estimated annual risk of evolution of AK to SCC is between 0.15% and 80% for patients with multiple AKs. Because it is not feasible to predict which AK lesions will become malignant, treatment of all AKs is recommended.[1]
- Current treatment for AK lesions includes cryotherapy (LN2) and topical 5-fluorouracil (5-FU). Patients have reported local adverse reactions with this therapy including erythema, dryness, pruritus, and irritation.[2]
- Vitamin D derivatives have demonstrated anti-proliferative properties in cancer treatment via stimulation of the vitamin D3 receptor, which can be found on keratinocytes.[3]
- Topical vitamin D has been shown to decrease the number of AK lesions. Recent research suggests that topical vitamin D derivatives may be efficacious in the treatment of AKs.[3]

METHODS

- This was a retrospective analysis of patients presenting with AKs in a clinical dermatology office setting.
- Three treatment groups were evaluated with 50 patients per group: 1) LN2, 2) LN2 with short-contact topical 5-FU 1% cream, 3) LN2 with short-contact topical 5-FU 1% cream and calcipotriene foam
- Lesion count was assessed and cryotherapy was administered on AK lesions at baseline visit. Patients in the groups #2 and #3 were then instructed to begin short-contact topical therapy cycles: nightly for 5 days on the face and 7 days on other affected areas, off for 2-week interval, and then repeat, with 5-FU (group #2) or both 5-FU and calcipotriene foam (group #3) Follow-up visits were scheduled for 1, 3, and 6 months.
- At each follow-up visit, AK lesion count was assessed and AK's treated with cryotherapy. Patients were also asked to report any side effects.
- Patient assessments and lesion counts were only performed at scheduled follow-up evaluation visits.
- ANCOVA analysis was used to adjust for imbalances in baseline AK lesion count.

RESULTS

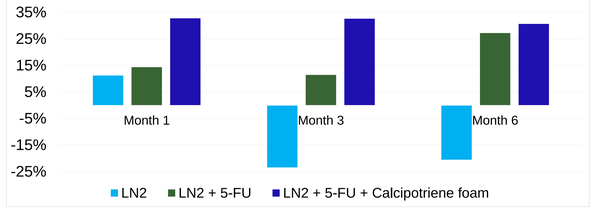
- A decrease in total AK lesion count was noted at months1, 3, and 6 using measures of central tendency, but a statistically significant decrease in total lesion count was only observed at month 6 compared to baseline count (p=0.03383).
- Upon further analysis, treatment with LN2 followed by short-contact topical 5-FU and calcipotriene foam (group #3) showed a greater mean decrease in number of AKs than treatment with LN2 alone (group #1) or LN2 followed by short-contact topical 5-FU (group #2) (Figure 1).
- Using Tukey Contrasts, a statistical difference in total AK lesions counts was only observed in group #3 (LN2 followed by short-contact 5-FU and calcipotriene foam) (p=0.0255) (Figure 2).

Figure 1. ANCOVA Summary Table 6 Months Treatment	p-value	Mean Change in Lesion Count	Confidence Interval (95%)
LN2	4.21e-07	17.212	11.055 – 23.369
LN2 + 5-FU	0.16420	-4.741	-11.467 – 1.985
LN2 + 5-FU + Calcipotriene foam	0.00952	-8.818	-15.415 – -2.221

Figure 2. Tukey Contrasts 6 Months Treatment	p-value
LN2 + 5-FU – LN2	0.3434
LN2 + 5-FU + Calcipotriene foam – LN2	0.0255

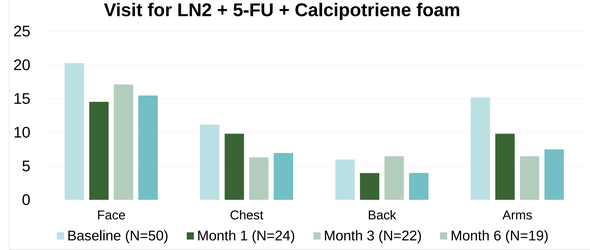
- A greater percent reduction in total AK lesion count was observed in patients treated with LN2 followed by short-contact combination therapy of calcipotriene foam with 5-FU than patients being treated with LN2 alone and LN2 followed by short-contact 5-FU (Figure 3).
- Compared with baseline, the mean lesion count decreased over the course of treatment at each body site evaluated (Figure 4).
- Two patients in group #1 (treated with LN2 alone), one patient in group #2 (treated with LN2 and short-contact topical 5-FU), and two patients in group #3 (treated with LN2 and short-contact topical calcipotriene foam with 5-FU) were determined to be noncompliant due to failure to maintain regularly scheduled follow-up visits at 1, 3, or 6 months.

Figure 3. Percent Reduction in Mean* Total Lesions by Treatment at 1-, 3-, and 6-Month Follow-Up Visits



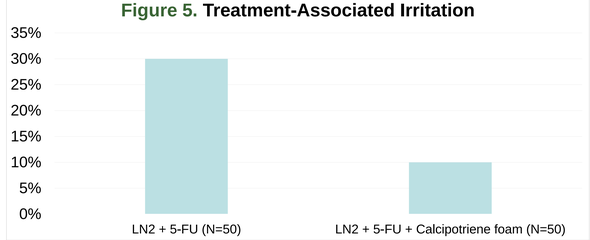
*Means after controlling for variations in baseline lesion count.

Figure 4. Mean Lesion Count Per Body Site at Each Visit for LN2 + 5-FU + Calcipotriene foam



- A total of fifteen patients (30%) treated with 5-FU cream and five patients (10%) treated with 5-FU cream and topical calcipotriene foam experienced some grade of irritation during their treatment course (Figure 5). Irritation was defined as patient-reported irritation due to the topical treatment.
- Reported symptoms of irritation included non-persistent mild erythema, dryness, and/or pruritus. No pain, scabbing, or erosion was reported.
- Cases of irritation resolved within two weeks of topical treatment discontinuation.
- No patients discontinued treatment due to irritation.

Figure 5. Treatment-Associated Irritation



CONCLUSIONS

- The combination of cryotherapy and short-contact treatment with 5-FU cream and topical calcipotriene foam (Group # 3) resulted in a statistically significant greater decrease in total AK lesions than LN2 alone (Group #1) or LN2 followed by short-contact with topical 5-FU (Group #2) at month 6 (p=0.00952).
- A reduction in mean total AK counts was observed at each body site in Group #3 in comparison to Group #1 or Group #2.
- Reductions in total mean AK lesion counts were demonstrated at months 1 and 3, with statistically significant decrease in total AK lesion count at month 6 (p=0.03383).
- Greater percent reduction in mean total AK lesion counts was also observed in patients treated with LN2 followed by short-contact combination therapy of calcipotriene foam with 5-FU than patients being treated with LN2 alone and LN2 followed by short-contact 5-FU.
- Treatment with LN2 followed by the short-contact treatment with calcipotriene foam in addition to 5-FU was associated with a lower rate of irritation (10%) than treatment with LN2 followed by short-contact treatment with topical 5-FU alone (30%).
- Irritation rates were also markedly lower than those reported in clinical trials (39%).[4] It is likely that the short-contact method of application resulted in tolerability improvement.
- Cryotherapy followed by short contact topical calcipotriene foam in combination with 5-fluorouracil cream may offer increased efficacy and safety in the treatment of actinic keratoses.
- Multicenter, randomized, placebo-controlled trials are needed to confirm these findings.

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