

Cost-efficient and non-surgical method for treating primary keratinocyte carcinomas with a combination of topical imiquimod, 5-fluorouracil and tretinoin

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BACKGROUND

- 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).
- 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, highlighting the considerable health and economic burden of these malignancies.
- Surgical excision including Mohs micrographic surgery (MMS) remain the standard for the treatment of NMSCs.
- 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 are often not FDA approved for the treatment of skin cancers, with limited/unknown clearance

OBJECTIVE

- 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.
- Effectiveness of the differing combinations of topicals was determined by their rates of tumor clearance over a three-year post-treatment period.

METHODS

STUDY DESIGN

- Identified 480 patients with 690 cases of NMSC (BCC or SCC) treated with topical combinations from 09/01/2009 to 12/31/2019.
- BCCs classified by superficial (sBCC), nodular (nBCC), morpheiform (mBCC).
- SCCs were subdivided into invasive (ISCC) and in situ (SCCIS).
- Inclusion Criteria:
 - Completed exactly 30 treatments of a combination of topical therapy with lesional cryotherapy occurring every two weeks (n=265 cases excluded)
 - Completed treatment protocol within 76 days after starting the first treatment (n=15 excluded).
 - 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

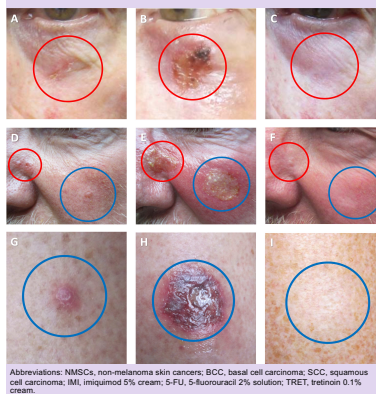
- Patients were prescribed one of three topical combination regimens:
 - IMI/TRET
 - 5-FU/TRET
 - IMI/5-FU/TRET
- Patients were instructed to apply the combination of topical medications to the tumor 5 days a week for 6 weeks with the following amounts:
 - 1/5 of a pea-sized amount of TRET
 - 1/5 of a packet of IMI
 - 1 drop of 5-FU
- Cryotherapy was performed for 1 second with 1-2 mm margins on the lesion before initiating topical treatment and at each visit (every two weeks).

STATISTICAL ANALYSIS

- Primary Outcome:** Tumor Clearance – lack of clinical evidence of persistence or recurrence following the completion of treatment to the follow-up examination of at least 3 years.
- Chi-Square Tests:** Compare clearance rates of treatment groups for each cancer subtype; Descriptive Statistics (Kruskal-Wallis Tests also used)
- Multivariate Logistic Regression:** Model likelihood of tumor clearance among cohort.
 - Adjusted for the treatment group, lesion of age, subtype, location, gender, smoking status, immunosuppression status, and quadratic transformation

- Total of 186 cases (97; BCC and 89; SCC) in 133 patients [37% women and 63% men; median (interquartile range) age, 77 (69, 83) years] met the inclusion criteria (Table 1).
- Cases of BCC:** 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).
- Cases of SCC:** 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).
- Multivariate logistic regression analysis demonstrated that, relative to the IMI/5-FU/TRET treatment approach, IMI/TRET (odds ratio, 0.05; 95% confidence interval, 0.00-0.99) and 5-FU/TRET (0.02; 0.00-0.45) were associated with lower likelihoods of lesion clearance.
 - Adjusted Probability of Tumor Clearance**
 - IMI/5-FU/TRET: 99.9%
 - IMI/TRET: 97.6%
 - 5-FU/TRET: 95%
- Morpheiform basal cell carcinoma had a lower probability of clearance (0.05; 0.00-0.72).
- Considering this, Mohs surgery should still be given the greatest consideration in the treatment of high-risk mBCC.
- With each case, every patient reported a cosmetically acceptable final appearance of their treated site (Figure 1).

FIGURE 1. Clinical images of NMSCs on the face before, during, and after treatments with combination topical therapies. (A) BCC (morpheiform; red circle) on the left superior cheek at the infraorbital margin. (B) BCC (morpheiform) 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.

RESULTS

Table 1. Patient characteristics by skin cancer and treatment group

| Variable | Overall (N = 186) [†] | Treatment Group | | | | | 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%) | — | — | — | |
| Morpheiform 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.

[†]N 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 [†] | Morpheiform | 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: nBCC, nodular basal cell carcinoma; mBCC, morpheiform basal 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 < .05. *P < .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, morpheiform 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.

CONCLUSIONS

- Our combination of IMI/5-FU/TRET resulted in a high overall clearance rate, which is consistent with this purported synergism.
- LIMITATIONS:**
 - Observational study with non-random assignment of patients to determine the efficacy of non-invasive therapies to treat NMSCs.
 - 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.
 - Further studies using these combinations for the treatment of NMSCs without cryotherapy and with telehealth are needed.
- 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.

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] | — |
| Morpheiform | 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 [‡] | 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 multivariate 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.

DISCUSSION

- Many patients declined surgical procedures for their NMSCs due to insurance issues or various reasons.
- COST ANALYSIS** (derived from Medicare rates (California, Area 72, 2019) and GoodRx)
 - Our therapies:
 - Office visits [99213*6] [\$79.43*6=\$476.58] + Cryotherapy [17000*6] [\$70.79*6=\$424.74] + Topicals [5-FU 2% solution (10 ml) – \$29.25; IMI 5% (30 pack) – \$28.18; TRET 0.1% cream (20 gm) – \$35.30] = **minimally cost around \$994.05.**
 - Implementation of a store-and-forward technology reduced visit costs from **\$476.58 to \$50.00.**
 - Other modalities:
 - Mohs surgery (2 stages) and flap reconstruction in a surgery center would cost **3-4 times (\$3131.58)** as much.
 - Radiation therapy (up to 17 fractionations) could be **13-14 times more expensive** than the combination modalities.
 - Interferon-alpha-2b injections can cost up to **2-3 times more** and requires weekly lab monitoring.
- MECHANISM OF ACTION**
 - Imiquimod binds to toll-like receptors on phagocytes and activates both the innate and adaptive immunity.
 - 5-fluorouracil induces a cytotoxic effect by forming metabolites that interfere with the synthesis and function of RNA and DNA.
 - Retinoids can downregulate keratinocyte differentiation and proliferation and enhance penetration of other topical medications by reducing epidermal hyperkeratinization.
 - Cryotherapy can increase the penetration of topical medications and is thought to release tumor antigens, stimulating an immune response that can be enhanced by the immunostimulant effects of anti-tumor topical medications.
- POTENTIAL SYNERGISM:** Combining these topical medications may be more effective than monotherapy.
 - Imiquimod induces the production of inflammatory cytokines that upregulate the enzyme thymidine phosphorylase, which is responsible for converting 5-fluorouracil to its active metabolite, therefore enhancing its therapeutic effects.