Triple therapy with intralesional 5-fluorouracil, chemowraps, and acitretin: A well-tolerated option for treatment of widespread cutaneous squamous cell carcinomas on the legs

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INTRODUCTION

Multifocal ill-defined and confluently distributed squamous cell carcinomas (SCCs) on actinically damaged legs can be therapeutically challenging. Additionally, patients may have treatment fatigue or be poor candidates for extensive surgery or radiation. Women, in particular, with multiple SCCs of the legs have this striking clinical phenotype.[1] Acitretin, intralesional 5-fluorouracil (5-FU), and 5-FU chemowraps have each alone shown efficacy in preventing or treating SCCs; however, their combined effectiveness has never been reported. We present 2 cases using combined triple therapy to treat widespread SCCs on the legs, illustrating a promising option for patients unwilling or unable to undergo surgery.

Abbreviations used:

5-FU:	5-fluorouracil
KA:	keratoacanthoma
SCCs:	squamous cell carcinomas

CASE 1

A 74-year-old woman presented with multiple biopsy-proven recurrent and new non–keratoacanthoma-type well-differentiated SCCs on the left leg despite excisions with clear surgical margins for 7 previous SCCs (Fig 1, *A*). She declined radiation and Mohs micrographic surgery. She received 0.5 mg/nodule of 500 mg/5 mL 5-FU intralesional injections and lower extremity chemowraps. Chemowraps consisted of 20 g of 5% 5-FU cream to the skin under occlusive zinc oxide–impregnated dressing in a single layer with 50% overlap, then a lightly compressive self-adhering bandage (ie, Unna boot), changed weekly. After 5 weeks of weekly 5-FU injections and chemowraps, her nodules began significantly flattening and acitretin, 25 mg/d, was added. Treatment was complicated by xerosis, mild alopecia, and a robust but expected ulcer development at injection sites (Fig 1, *B*). Her nodules resolved and ulcers re-epithelialized by 6 months (Fig 1, *C*).

CASE 2

A 60-year-old woman previously treated with psoralen and ultraviolet A for 7 years for psoriasis presented with 16 nodules with several representative nodules biopsied as well-differentiated invasive SCCs over a background of actinically damaged legs (Fig 2, *A*). These nodules were separate from her 10 previous Mohs surgical scars and sites treated with topical 5-FU and imiquimod for previous SCCs. She declined further surgical or radiation treatment, and started weekly 5-FU injections (0.1-0.5 mg/nodule), chemowraps, and acitretin, 25 mg/d.

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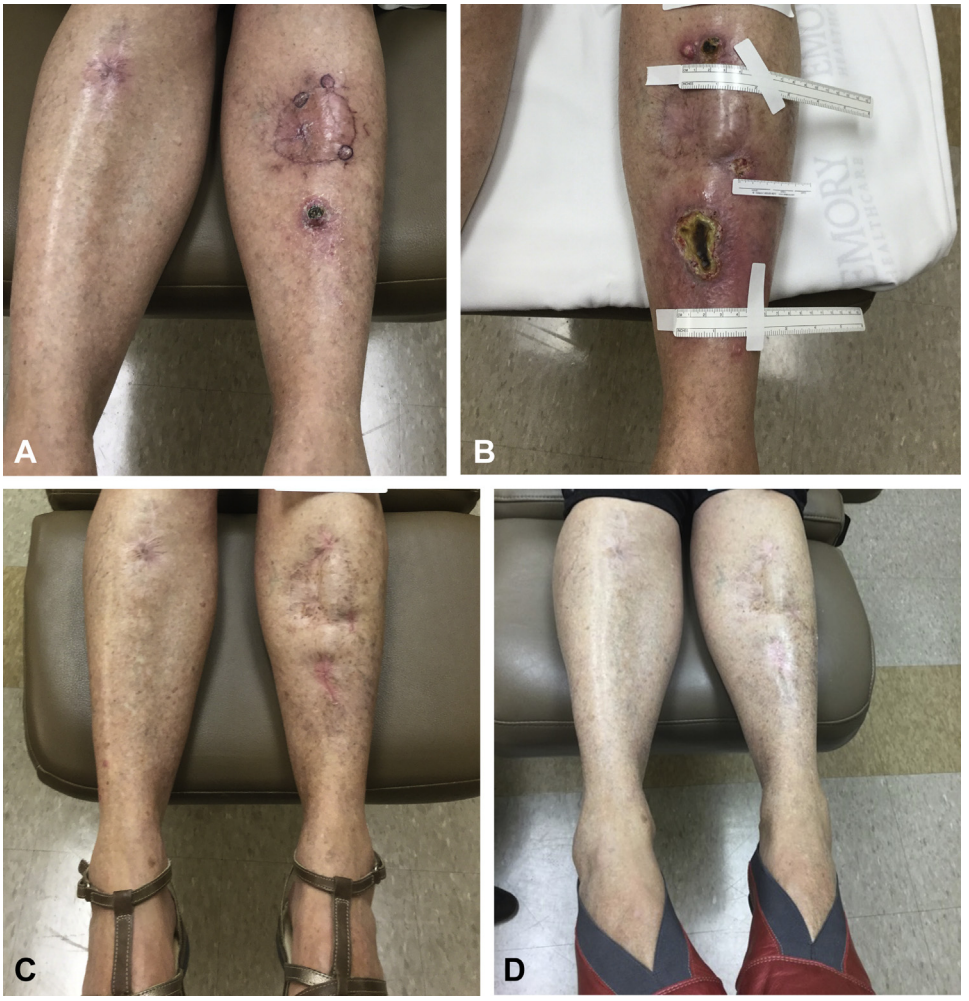

Fig 1. Patient described in Case 1. **A**, Initial presentation with multiple squamous cell carcinomas on the left leg. **B**, After the fifth week of weekly 5-fluorouracil injections and chemowrap placement; also when patient initiated acitretin. **C**, After six months of acitretin; ulceration has completely healed without new nodules or erosions. **D**, One year after triple therapy completion.

By 4 weeks, she had a robust response to topical 5-FU, making her legs erythematous, edematous, and painful (Fig 2, *B*). She was given 2 days of acetaminophen-oxycodone 5 mg/325 mg every 4 hours as needed and treatment withheld. Her course was complicated by an infected ulcer that resolved with cephalexin. In 1 month, her nodules almost completely clinically resolved, and triple therapy was restarted for 2 more months (Fig 2, *C*).

SUMMARY

Neither patient experienced myelosuppression. Acitretin was briefly withheld when the latter patient had hypercholesterolemia until pravastatin was started and cholesterol normalized. Both patients tapered down to acitretin, 10 mg/d after 4 months. After 3 additional months, they tapered to 10 mg every other day for prevention for up to 10 months. At 1-year follow-up, both patients remained without clinical recurrence (Figs 1, *D* and 2, *D*)

DISCUSSION

Multifocal SCCs on the legs are most often seen in immunocompromised patients (eg, solid organ transplant recipients and chronic lymphocytic leukemia patients) or those with previous exposure to arsenic, psoralen and ultraviolet A, or ionizing radiation. Nonimmunocompromised patients can also develop this presentation, as in our first case. The first case noted significant improvement only after acitretin was started, suggesting a synergistic benefit

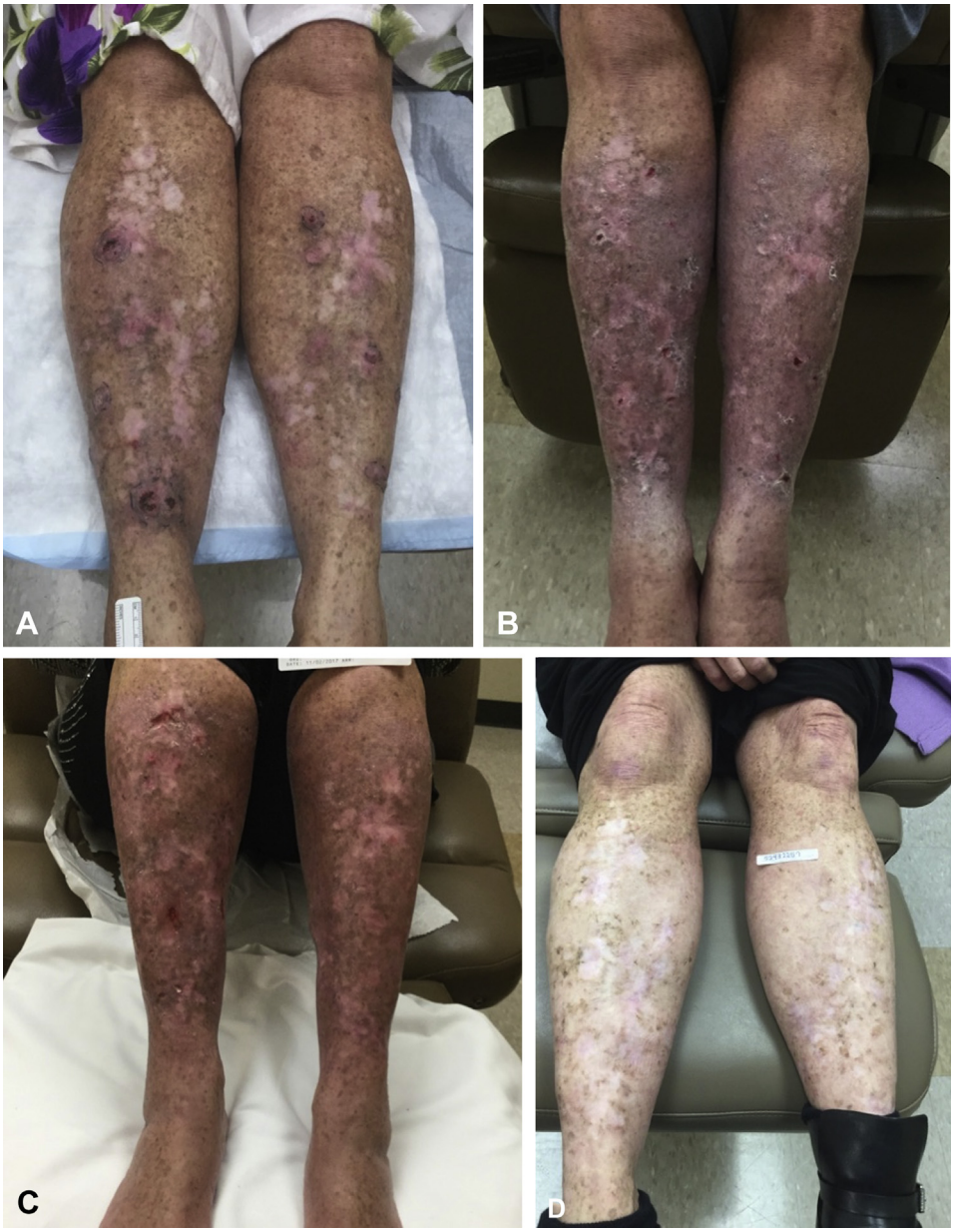

Fig 2. Patient described in Case 2. **A**, Initial presentation with multiple SCCs on bilateral legs. **B**, After the fourth week of weekly 5-FU injections and chemowraps and concurrent acitretin therapy. **C**, At 7 months, nodules had completely flattened and ulcers continued to re-epithelialize; 5-FU was injected into 2 remaining small nodules on the right calf, and chemowrap application frequency was tapered down to 1 week per month. **D**, One year after triple therapy completion.

of combining acitretin with intralesional 5-FU and chemowraps.

Intralesional 5-FU and chemowraps have been used for SCC treatment[2,3] and acitretin for prevention.[4] A PubMed search from 1970 until April 2019 using various combinations of the terms *acitretin* or *retinoid* and *fluorouracil* or *chemotherapy* and *leg* or *extremity* finds that their combination has never been reported as a therapeutic option for SCCs.

Intralesional 5-FU has been used off-label for nonmelanoma skin cancers.[5,6] Systemic side effects or risks in topical and intralesional form are exceedingly rare, but local reactions are common (eg, erythema, blistering, erosions, and burning). A comprehensive literature review found that

intralesional 5-FU resulted in positive treatment success for keratoacanthomas (KAs) (66 of 68 resolved, 97%) and SCCs (24 of 25 resolved, 96%) with only local and no systemic side effects.[5,6] Dose varied based on tumor size but were approximately 0.1 to 2 mL per lesion weekly, for 4 to 8 total treatments. Maximal recommended dosage is 800 mg/d.[6]

Chemowraps with 5-FU have demonstrated successful response for actinic keratoses and SCCs.[7] Overuse of 5-FU, including one report of systemic toxicity with chemowraps, must be kept in mind, with myelosuppression and gastrointestinal toxicity being the most commonly observed manifestations of systemic toxicity.[3] In the particular case of a patient who had systemic toxicity with chemowraps, the proposed etiology was that her chemowraps were continued in the setting of widespread skin erosion and ulceration, which has shown hematogenous absorption of 5-FU approaching 60%.[8]

Our cases highlight not only a practical and tolerable approach with positive responses for widespread SCCs on the legs at up to 1-year follow up, but also a nonaggressive measure to decrease morbidity in these patients. Additionally, a case series of 30 SCCs in 6 women were reanalyzed, histopathologically showing that 16 of the lesions resembled keratoacanthoma-like squamous proliferations all lacking TP53 mutations that 10 of the 14 actual SCCs had. This finding suggests that some of the squamous proliferations on the legs of women might be more akin to KA or reactive phenomena than SCC.[1] Combining the results of our patients with those of that series suggests that therapeutically aggressive procedures such as Mohs micrographic surgery and standard surgical excision may not be necessary for patients of this similar clinical phenotype. Another case series found recurrence of KAs at the surgical margin in 3 patients after they were appropriately treated surgically, suggesting that these KAs were rather reactive and may worsen in the setting of repeated surgical trauma.[9] Another case showed that a recurrent KA on the leg managed with Mohs micrographic surgery and left to heal with second intention successfully healed without recurrence, suggesting that potential trauma from suture placement may induce the formation of KAs.[10] Our regimen minimizes that postulated risk factor for recrudescence.

This triple therapy approach can be considered when patients are poor candidates for or desire no surgical or radiation treatment. Adequate pain control and infection surveillance are imperative to maximize patient adherence and safety. We encourage larger controlled studies to better characterize the regimen, efficacy, complication rate, and durability of this option.

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