Cutaneous T-Cell Lymphoma Treatment: Case Series of Combination Therapy With Intralesional Injections of 5-Fluorouracil and Topical Imiquimod

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PRACTICE **POINTS**

- Cutaneous T-cell lymphoma (CTCL) is a chronic lymphoma affecting the skin with limited durable effective skin-directed therapies.
- Combination intralesional 5-fluorouracil and topical imiquimod is a well-tolerated, fast, convenient, and durable therapy for recalcitrant thick plaques and tumors of CTCL.
- This regimen may be utilized as monotherapy or as the skin-directed component of combination therapy based on disease stage.

Cutaneous T-cell lymphoma (CTCL) is a chronic form of skin cancer. Skin-directed therapies rarely achieve complete clearance of lesions, and recurrences are frequent. In this case series, 9 patients with stage IA to IVA2 CTCL received intralesional (IL) therapy with 5-fluorouracil (5-FU) and imiquimod (IMQ) cream 5% daily to recalcitrant plaques and tumors. All 9 patients attained a complete response (CR) with no recurrences reported and no severe side effects. We find that combination IL 5-FU and IMQ cream 5% daily is a well-tolerated, effective, and durable skin-directed therapy for recalcitrant plaques and tumors in CTCL.

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Cutaneous T-cell lymphoma (CTCL) is a diverse group of skin-homing T-cell neoplasms with a wide array of clinical presentations, immunohistopathologic subtypes, and prognoses. The age-adjusted incidence of CTCL in the United States is 6.4 per million individuals.[1] In the early stages of CTCL, the malignant lymphocytes are isolated to the skin, while more advanced disease involves metastatic spread to the lymphatic and peripheral blood compartments. Mycosis fungoides (MF) is the most common subtype of CTCL, comprising roughly 50% of all cases. The etiology of CTCL and MF remains poorly understood and no unifying driver mutation has been identified.[2] However, recent sequencing efforts have revealed recurrent genomics alterations primarily in 3 pathways: constitutive T-cell activation, resistance to apoptosis/cell-cycle dysregulation, and DNA structural/gene expression dysregulation.[3-8] These studies, among others, support the assertion that CTCL may be an epigenetic phenomenon.[9-14]

Most patients with MF will experience an indolent course of skin-limited disease with a favorable prognosis and a 5-year survival rate of 88%.[15-17] A large study of patients with MF (N=525) followed for more than 40 years determined that approximately 20% of early-stage (IA-IIA) patients with MF progress to develop tumors, metastasis to the lymphatic tissue, and/or leukemic blood disease.[18]

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Drs. Lindberg and DiLorenzo report no conflict of interest. Dr. DeSimone is a speaker for Helsinn and a consultant for Regeneron.

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Cutaneous T-cell lymphoma is a chronic disease, and most treatment responses are partial and short-lived. Allogenic hematopoietic transplantation is the only potentially curative option, and all other therapies are aimed at arresting progression and achieving remission.[19] Skin-directed therapies include topical steroids, topical nitrogen mustard, phototherapy, and radiation. Systemic therapies such as oral retinoids, chemotherapy, and immunotherapy may be used alone or in combination with skin-directed therapies based on the overall disease stage and clinical presentation. Unfortunately, complete response (CR) to therapy is rare and fleeting, and most patients require multiple sequential treatments over their lifetimes.[20]

Across all stages of CTCL, there is a therapeutic push to combination and immune-based therapies to achieve more durable responses. The imidazoquinolines are a family of toll-like receptor (TLR) agonists including imiquimod (TLR7) and resiquimod (TLR7 and TLR8). Imiquimod (IMQ) is a topical immunomodulator, which increases the local cytotoxic helper T-cell profile (T_H1 marked by IFN-α, tumor necrosis factor α, IL-1α, IL-6, and IL-8), thereby enhancing both humoral and innate immune responses targeting tumor cells.[21-23] Several small studies evaluating topical TLR agonists have documented efficacy in patients with early and advanced stages of CTCL.[24-34]

Skin-directed chemotherapy using 5-fluorouracil (5-FU) has shown activity against many cutaneous malignancies. 5-Fluorouracil is an antimetabolite drug that inhibits thymidylate synthase, resulting in interrupted DNA and RNA synthesis and leading to an apoptotic cell death (Figure 1). It has been administered via intravenous, oral (prodrug), intralesional (IL), and topical routes with well-documented success in treating cutaneous squamous cell carcinoma, keratoacanthoma, basal cell carcinoma, and precancerous actinic keratosis.[35] As a topical, 5-FU has been shown to provide a good response in 6 patients with early MF.[36] In late-stage MF, 5-FU has been used in combination with methotrexate as an infusion.[37] We present a single-center case series of 9 patients with CTCL who received combination IL 5-FU and IMQ cream 5%.

Methods

Patient Selection—Patients were selected from our multidisciplinary CTCL subspecialty clinic at the Inova Schar Cancer Institute (Fairfax, Virginia). Patients with single to few recalcitrant CTCL plaques or tumors that were symptomatic or otherwise bothersome were included. All patients had at least 2 prior skin-directed therapies that failed, and many had advanced-stage disease requiring systemic therapy. All patients provided verbal consent.

Study Materials and Evaluations—Patients received IL injections of 5-FU 50 mg/mL. The volume injected was approximately 0.2 cc per cubic centimeter of lesion tissue. Injections were repeated at 2- to 3-week intervals until the target lesions achieved an acute hemorrhagic phase characterized by erosion, flattening, and crust formation. The total number of serial injections administered ranged from 1 to 5. The patients concomitantly treated all lesions with IMQ cream 5% daily for a duration of 2 to 3 months.

Medical photography and physical examination were performed every 2 to 3 weeks until the hemorrhagic phase resolved and treated sites re-epithelialized. Index lesions were assessed using the Composite Assessment of Index Lesion Severity (CAILS) score by a single investigator for all patients.[38] Scores were retrospectively assigned using the investigator's detailed physical examination descriptions and extensive medical photography. Any hyperpigmentation was scored as residual disease, despite the fair interpretation of it as procedure-related postinflammatory dyspigmentation. Complete response was strictly defined as a CAILS score of 0. The patients were screened

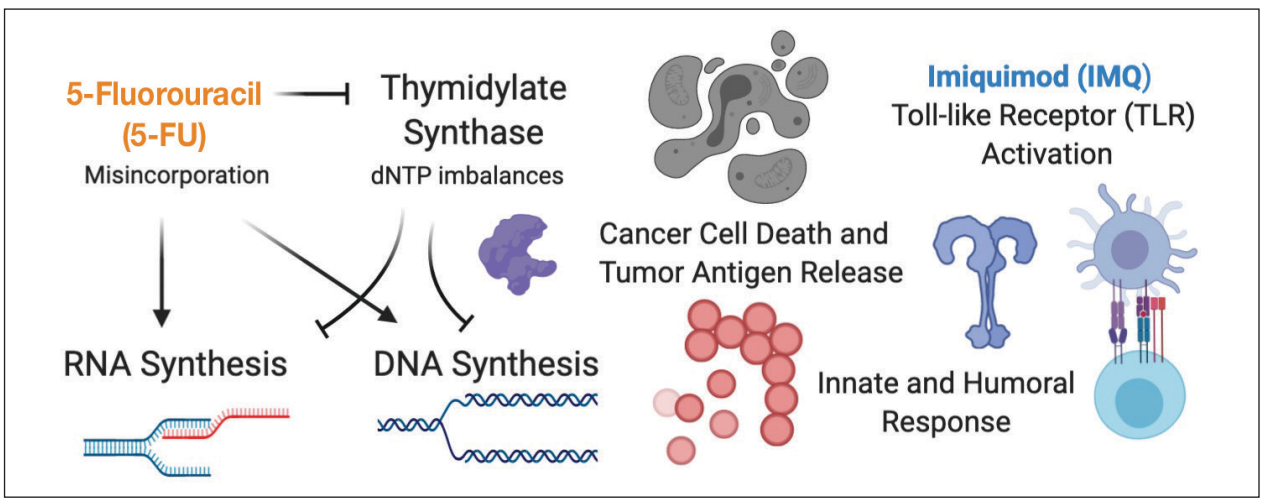

FIGURE 1. Proposed mechanisms of action for study treatments. A cartoon depiction of 5-fluorouracil (5-FU) and imiquimod (IMQ) mechanisms of action showing the activity of both drugs individually and how they may act synergistically to improve efficacy when used together. dNTP indicates deoxynucleotide triphosphate.

for possible systemic effects of IMQ, including the presence of fever, chills, fatigue, and myalgia. Patients were evaluated every 6 to 12 weeks as a standing follow-up.

Statistical Analysis—Reductions were calculated using local regression from baseline to the 4- to 7-week follow-up. Patients with multiple lesions had their CAILS score averaged at each time point in aggregate and individually. The 95% CIs were calculated as 2 SDs from the composite and individual means.

Results

Nine patients aged 28 to 91 years (median age, 66 years) with CTCL stages IA to IVA2, who had lesions located throughout their body, achieved CR; 3 patients were female (Table 1). The most common phenotype was $CD8^+$ (n=3). All patients had at least 2 prior skin-directed therapies at treatment sites that failed, and 1 patient had 7 prior treatments that failed. Prior treatments included a variety of modalities, including all standard-of-care

TABLE 1. Patient Characteristics

Patient no.	Age, y	Sex	Stage (entry)	Lesion location/ characteristics	Immunophenotype	Prior treatment (systemic and topical)
1	91	F	IB	Groin/2.6×2.5-cm hemorrhagic nodule	Double negative ($CD4^-$, $CD8^-$)	PUVA, pralatrexate, methotrexate, gemcitabine
2	68	M	IIB	Thigh/5.1×4.7-cm erythematous plaque; thigh/1.6×1.5-cm erythematous nodule; thigh/2.1×1.9-cm erythematous to hyperpigmented plaque	$CD30^+$	Brentuximab, mechlorethamine gel, participant in FLASH trial
3	66	F	IIB	Shoulder/6.2×4.8-cm hemorrhagic plaque	$CD8^+$, large cell transformation $CD30^-$	Doxorubicin liposomal, romidepsin, mogamulizumab, gemcitabine
4	56	M	IA	Arm/6.5×6.5-cm annular erythematous plaque	Double negative ($CD4^-$, $CD8^-$), large cell transformation	History of stage IIIB status after allogenic stem cell with recurrent stage IA
5	58	F	IV	Cheek/2.8×2.8-cm erythematous thin tumor	$CD4^+$	Prednisone, vorinostat, gemcitabine, and continued use of romidepsin throughout study
6	70	M	IB	Ear/2.5×3.4-cm eroded plaque	$CD8^+$	Triamcinolone, clobetasol propionate cream, pralatrexate
7	57	M	IIB	Hand/4.0×4.0-cm tumor; wrist/3.0×3.0-cm tumor	$CD30^+$ large cell transformation	Brentuximab, bexarotene, nivolumab, mogamulizumab, clobetasol, NB-UVB, total skin electron beam therapy
8	81	M	IIB	Neck/6×3.8-cm firm erythematous tumor; neck/2.5×2.5-cm firm erythematous tumor; neck/3.2×3.3-cm firm erythematous tumor	$CD4^+$	Pralatrexate, doxorubicin, mechlorethamine gel, bexarotene, nivolumab
9	28	M	IA	Thigh/3.5×3.5-cm thick indurated erythema tous plaque; leg/2.4×2.6-cm thick indurated erythematous plaque	$CD8^+$, TIA-1	Clobetasol propionate, mechlorethamine gel

Abbreviations: F, female; M, male; NB-UVB, narrowband UVB; PUVA, psoralen plus UVA.

options and enrollment in clinical trials. One patient died from pneumonia following CR (Table 2). Seven patients had previously received systemic therapy for CTCL, and 1 patient was stable on romidepsin during our study. In patients who received more than 1 injection of 5-FU—1 injection: 3 patients; 2 injections: 3 patients; 3 injections: 1 patient; 4 injections: 1 patient; 5 injections: 1 patient—injections were spaced by 2 to 3 weeks. There was 1 patient who initially had an inadequate dosing of IL 5-FU and was restarted 14 months later; this was the patient with 5 total injections. This occurred in one of the first patients in the study, who presented with a facial lesion. The investigator used approximately 0.02 cc per cubic centimeter (dose reduction of nearly 90%), which was inadequate and did not achieve the requisite hemorrhagic phase.

Treatment was well tolerated overall. In all cases, a hemorrhagic phase was achieved, characterized by erosion and crusting that was rated as mildly uncomfortable by 7 patients and moderately uncomfortable by 2 patients. In total, 15 lesions in all 9 patients achieved a CR within 24 weeks of the final injection. The longest treatment course required 12 weeks of therapy with IMQ and 5 IL injections of 5-FU. The fastest CR was achieved in patient 6 within 6 weeks following a single IL injection of 5-FU and 2 applications of IMQ. The average time to CR was 14.78 weeks (95% CI, 1.75-27.81)(Figure 2), and the time to CR ranged from 4 to 24 weeks. On average, patients achieved more than 50% reduction in CAILS score by 3.53 weeks (95% CI, 1.55-5.51) and nearly a 4-fold (74.7%) reduction at the time of initial follow-up (occurring at 4–7 weeks). By 7 weeks, patient 3 had the most modest improvement in CAILS score with a 2.75-fold reduction, while patient 5 had the largest decrease with a 5-fold reduction. Figure 3 shows representative clinical photographs of 2 patients before and after treatment, with all patients having similar results.

Comment

Cutaneous T-cell lymphoma is a chronic skin cancer with a pattern of limited response to therapy and frequent recurrence. Currently available skin-directed therapies function as temporizing measures rather than curative treatments. Immunotherapy offers the promise of lasting disease control even after cessation of treatment, as it may essentially awaken cutaneous immune surveillance to malignant lymphocytes.

Several small observational studies have evaluated topical IMQ and TLR agonist therapy in CTCL. The construct of prior reports varies widely, including many different pretreatments, dosing schemes, and follow-up periods.[24-33] Dosing intervals with IMQ ranged from daily to 3 times per week and treatment duration from 2 weeks to 1 year. Complete response rates from 50% to 100% were reported, and partial responses were observed in all but 1 patient, with recurrence-free follow-up ranging from 6 months to 8 years. Comparatively, combining IL 5-FU and IMQ appears to be at least as effective as IMQ alone or in other sequential treatments and combinations.[24-33]

TABLE 2. Patient Treatment Course

Patient no.	Treatment	Time to CR	Maximum follow-up period and lesion status
1	IL 5-FU×1 + IMQ daily 2 wk	10 wk	55 months, CR
2	IL 5-FU×3 + IMQ daily 11 wk	18 wk	57 months, CR
3[a]	IL 5-FU×2 + IMQ daily 6 wk	12 wk	7 months, CR
4	IL 5-FU×1 + IMQ daily 2 wk	24 wk	47 months, CR
5	IL 5-FU×1 + IMQ daily 2 wk	9 wk	3 months, CR
6	IL 5-FU×1 + IMQ daily 2 wk	4 wk	10 months, CR
7	IL 5-FU×2 + IMQ daily 6 wk	12 wk	43 months, CR
8	IL 5-FU×2 (every 3 wk) + IMQ daily 6 wk	18 wk	26 months, CR
9	IL 5-FU×4 + IMQ daily 11 wk[b]	24 wk	33 months, CR

Abbreviations: 5-FU, 5-fluorouracil; CR, complete response; IL, intralesional; IMQ, imiquimod.

[a]Patient died.

[b]The first injection in this patient was an inadequately low dose and subtherapeutic; therefore, the patient required 4 additional injections of the standard dose.

Resiquimod, an experimental TLR7/8 agonist, has shown promising results in CTCL. Rook et al[34] conducted a phase 1 trial of topical resiquimod in 12 early-stage patients with CTCL, all of whom responded to therapy. Two patients achieved CR, and 9 achieved a partial response, including 5 patients with the folliculotropic subtype. Interestingly, an abscopal effect was observed in 92% (11/12) of patients. Molecular evidence of reduction of the malignant clone was observed in 90% of patients via high-throughput sequencing of lesional tissue.[34] These exciting findings suggest that topical immune therapy with TLR agonists may achieve robust, sustained, and possibly global disease control in CTCL.

Topical therapies are limited by depth of absorption, which can present a barrier to using these treatments for thicker plaques and tumors. Combining IL and topical routes was critical in our study design. Having good clinical experience using IL 5-FU in nonmelanoma skin cancers, we hypothesized that IL 5-FU would achieve a cytotoxic response through the full depth of thicker lesions and erode the surface of these lesions to facilitate penetration of topical IMQ. We additionally hypothesized that the combination of mechanisms of action would lead to an additive or synergistic response (Figure 1). By first inducing apoptotic cell death via 5-FU, we hoped to spill malignant lymphocyte neoantigens. Coupling that antigen exposure with an enhanced T_H1-biased immune response driven by IMQ should facilitate tumor clearance and immune education against malignant T cells.

In our case series, all 15 lesions in 9 patients completely cleared, and no recurrences were observed at 26-month follow-up. No patients encountered any major adverse events, and the procedure was well tolerated by all.

Study Limitations—Limitations of this small study certainly exist. It is impossible to prove that our mechanistic theory is accurate given our strictly clinical assessment tools. We speculate that if our results had been achieved with IL 5-FU alone, future investigation with a prospective study using multiple treatment arms including a control would be warranted. Kannangara et al[36] reported the use of topical 5-FU for MF and the drug's utility in either topical or IL routes for CTCL, which deserves further study. It is less likely that results were achieved exclusively by IMQ because of the rapid tissue breakdown observed in the acute hemorrhagic phase. This phenomenon is best explained by the sudden apoptosis caused by DNA intercalation from 5-FU. The follow-up period is not uniform because this was a rolling enrollment study. Follow-up will be ongoing, and we aim to assess all patients up to at least the 5-year point. A final limitation of this study is the purely clinical end point. In the future, pretreatment and posttreatment biopsies would be useful in assessing proof of histologic response, and high-throughput sequencing may be used to look for molecular clearance via liquid biopsy. Lastly, careful observation for possible abscopal effect using the Severity-Weighted Assessment Tool score would be interesting and potentially contributory to our understanding of the impact of topical immune therapy on cutaneous tumor surveillance.

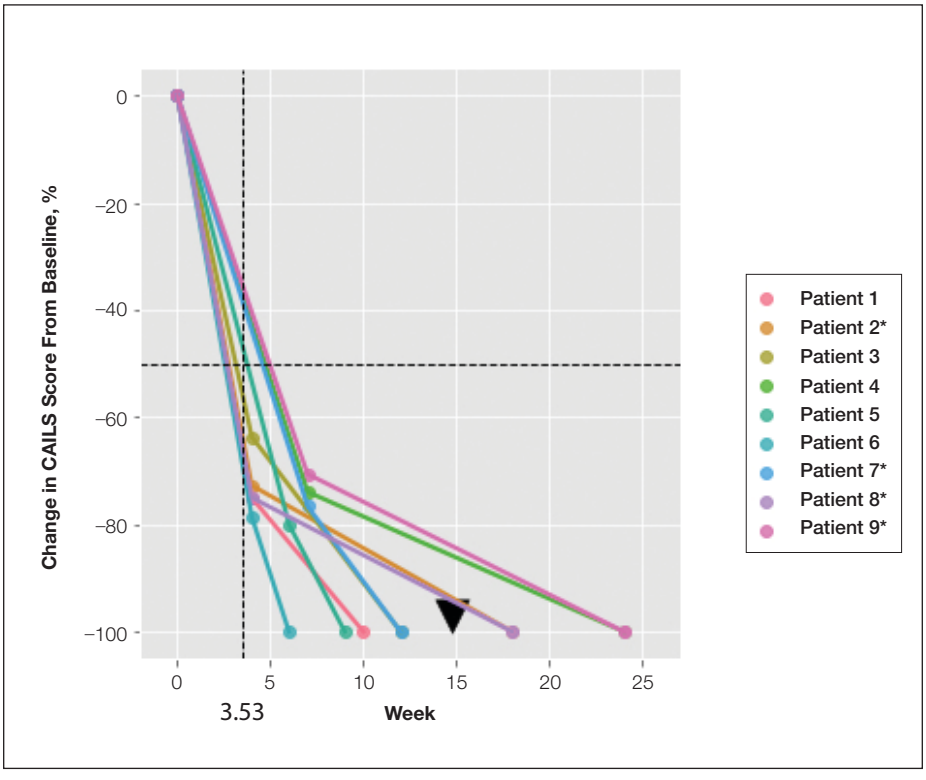

FIGURE 2. Composite Assessment of Index Lesion Severity (CAILS) score plots. Scores for each patient show percentage change from baseline. Asterisk indicates patients with more than 1 lesion; an average was calculated for CAILS score at each time point and was used in determining complete response and reduction times. The dashed black horizontal line depicts a 50% reduction in CAILS score from baseline, and the dashed black vertical line shows the average 50% reduction in CAILS score across all patients. The black arrowhead is the average complete response across all patients.

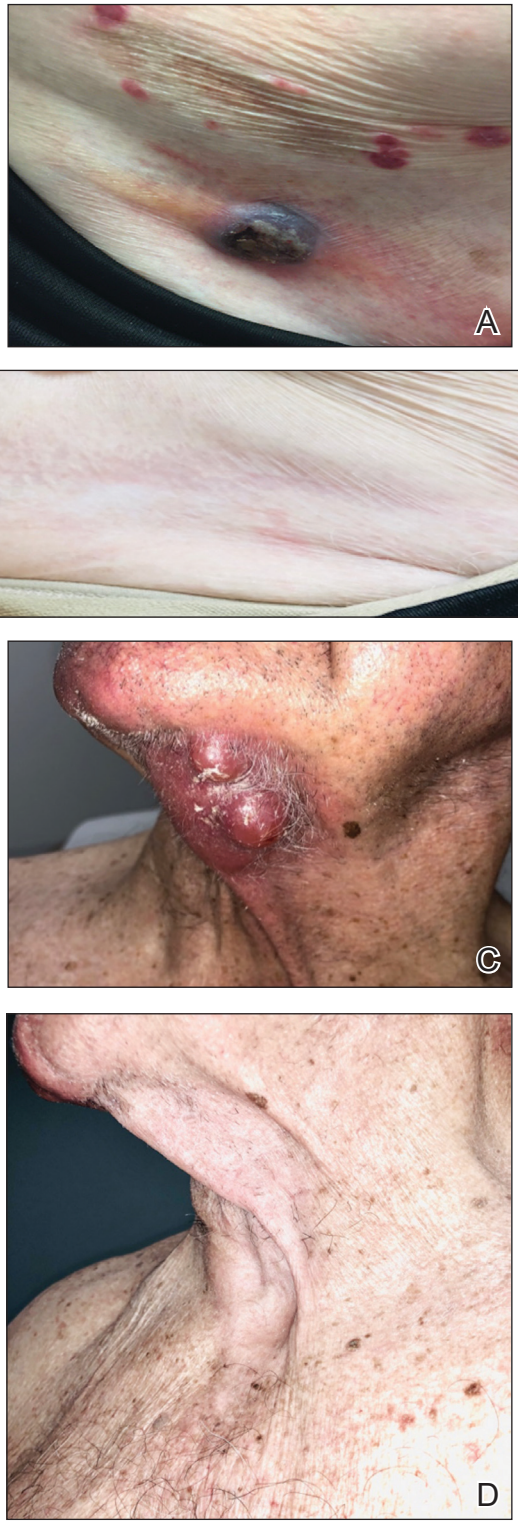

FIGURE 3. A, Patient 1 before treatment with the presence of a cutaneous T-cell lymphoma nodule near the inguinal crease. B, This patient showed complete response after 10 weeks of treatment with intralesional (IL) 5-fluorouracil (5-FU) and imiquimod. C, Patient 8 before treatment with a cluster of tumors on the neck 2.5 to 6 cm in diameter. D, The patient showed a complete response at 18 weeks to 2 serial injections of IL 5-FU and daily topical imiquimod.

Conclusion

Combination IL 5-FU and topical IMQ is a well-tolerated, effective, and durable therapy for recalcitrant thick plaques and tumors of CTCL. This treatment is convenient and cost-effective. The procedure is performed in less than 5 minutes in an outpatient dermatology clinic. All patients received full insurance coverage for both drug and procedure fees under Medicare and commercial carriers.

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