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CASE REPORT

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Low-Dose Intralesional Recombinant Interferon-α2b in the Treatment of Mycosis Fungoides

Jamie Katy Hu[a], Kacie Carlson[b], and Michael Girardi[b,*]

[a]*Yale School of Medicine, New Haven, CT;* [b]*Department of Dermatology, Yale School of Medicine, New Haven, CT*

Mycosis fungoides (MF), the most common form of cutaneous T-cell lymphoma (CTCL), is characterized by malignant CD4+ skin-homing T-cells that drive formation of cutaneous patches, plaques, and/or tumors. MF's known immunogenicity makes it an ideal candidate for local immunotherapy. Recombinant human leukocyte interferon-α2 (rIFN-α2) has well-established immunomodulatory, antiproliferative, and antitumor effects; and relatively low levels of endogenous IFN-α have been observed within MF lesions. As a systemic therapy delivered via subcutaneous (SC) or intramuscular (IM) injection, rIFN-α2 has previously shown efficacy against MF. Due to high levels of toxicity associated with the systemic dosing required for improvement of disease, rIFN-α2 has had limited use in the treatment of MF. For these reasons, we sought to deliver rIFN-2 as a local immunotherapy, and herein describe two cases of MF successfully managed with intralesional injections of low-dose rIFN-α2. With limited reporting in the medical literature, intralesional injection of rIFN-α2 has shown efficacy, but with high frequency of associated systemic side effects. Towards a better tolerated, localized immunotherapy, we initiated treatment in two MF patients with low dose (0.5 MU) rIFN-α2 per injection that led to marked responses, and subsequent dosing to 1.0 MU ultimately led to complete resolution of the treated lesions without the generalized side effects observed with systemic administration of rIFN-α2. These cases suggest that low-dose intralesional rIFN-α2 may be an efficacious and well-tolerated local immunotherapy for early stage MF, providing a therapeutic option for the management of chronic, recalcitrant lesions.

INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) represent a class of non-Hodgkin lymphomas of typically CD4+ skin-homing malignant T-cells. Mycosis fungoides (MF) is the most common subtype, manifesting clinically as cutaneous patches, plaques, and/or tumors. The accessibility of these lesions allows for skin-directed therapies. Characterized by significant immunogenicity, MF lesions further present the opportunity for local, immune-based

*To whom all correspondence should be addressed: Michael Girardi, M.D, 333 Cedar St, LCI 501, PO Box 208059, New Haven, CT, 06520; ORCID iD: 0000-0002-7377-0271, Tel: 203-785-4092, Fax: 203-776-6188, Email: michael.girardi@yale.edu.

Abbreviations: CTCL, cutaneous t-cell lymphoma; MF, mycosis fungoides; rIFN-α2, recombinant interferon-α2; SC, subcutaneous; IM, intramuscular; NB-UVB, narrow band UVB.

Keywords: cutaneous t-cell lymphoma (CTCL), mycosis fungoides (MF), intralesional, recombinant interferon-α2, local immunotherapy

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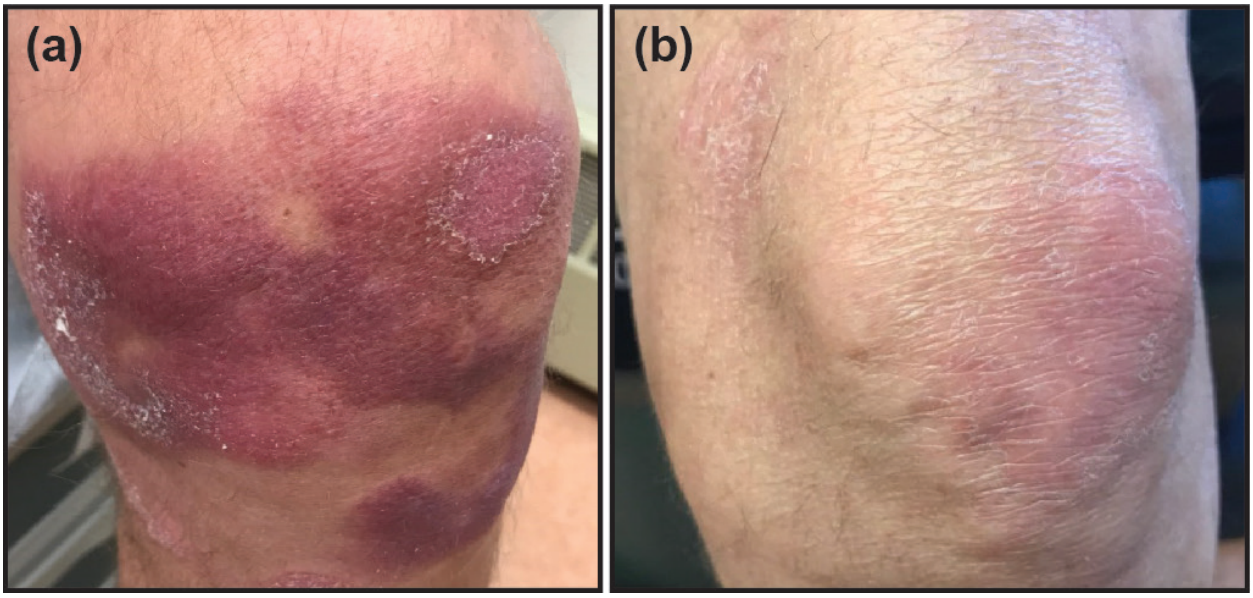

Figure 1. Clinical findings on the left medial knee of a patient with stage IB MF. (**a**) Thick red-violaceous coalescing plaques before and (**b**) after treatment with intralesional rIFN-α2.

treatment [1].

Recombinant human leukocyte interferon-α2 (rIFN-α2) is a systemic immunotherapy that has previously demonstrated therapeutic efficacy against CTCL, and a variety of other malignancies including other lymphomas, hairy cell leukemia, and chronic myelogenous leukemia [2]. Intralesional injection of rIFN-α2 has also been reported in a limited number of MF stage I and II patients, universally resulting in partial or complete resolution of the treated lesions both clinically and histologically [2-4]. These reports describe dosing of rIFN-α2 in the range of 1-2 MU per injection, three times weekly (3x/wk) for 4-12 weeks, often resulting in systemic side effects such as fevers, myalgias, nausea, and leukopenia [3].

Herein, we report two MF patients within whom intralesional injections of rIFN-α2 into refractory lesions were initiated at 0.5 MU 3x/wk, resulting in substantial clinical benefits without generalized side effects. Thereafter, increasing to 1.0 MU 3x/wk intralesionally resulted in complete resolution of treated lesions, also without the symptoms observed with the higher dosing of systemically administered rIFN-α2.

REPORT OF TWO CASES

Case 1: A 73-year-old man with stage IB (T1 N0 M0) MF was well-controlled for 8 years with a regimen of weekly narrow-band UVB (NB-UVB), topical bexarotene gel, topical mechlorethamine gel, and topical imiquimod to thicker lesions. However, the patient ultimately developed thick red-violaceous coalescing plaques on his left medial knee refractory to his treatment course (Figure 1a).

The patient injected 0.5 MU of rIFN-α2b 3x/wk directly into the thickest lesions on his left medial knee. Starting from the perimeter, the patient delivered the intralesional rIFN-α2b in multiple injections rotating throughout the thickest lesions, distributing the medication as evenly as possible. This resulted in marked improvement over 8 months, with a ~75% reduction in size and thickness of the plaques, without any reported systemic symptoms. The dose was then increased to 1 MU of rIFN-α2b 3x/wk for 3 months, which induced complete resolution (Figure 1b). While the patient reported mild fatigue with 1 MU dosing, this symptom completely resolved by moving the injections to the evening. Additionally, the patient did not require maintenance IM or SC injections of rIFN-α2b following the resolution of the injected lesions.

Case 2: A 64-year-old man with stage IIB (T3 N0 M0) MF was managed over a 2-year period with NB-UVB, oral bexarotene, topical imiquimod, and clobetasol, with good response except for localized, persistent lesions located on his back (Figure 2a).

His persistent lesions were similarly treated with 0.5 MU of intralesional rIFN-α2b 3x/wk. After 3 months of treatment, the lesions had diminished in both size and thickness, resulting in several much smaller residual lesions. The remaining lesions on his back were then treated with 1 MU of intralesional rIFN-α2b 3x/wk which further improved their appearance and size, ultimately

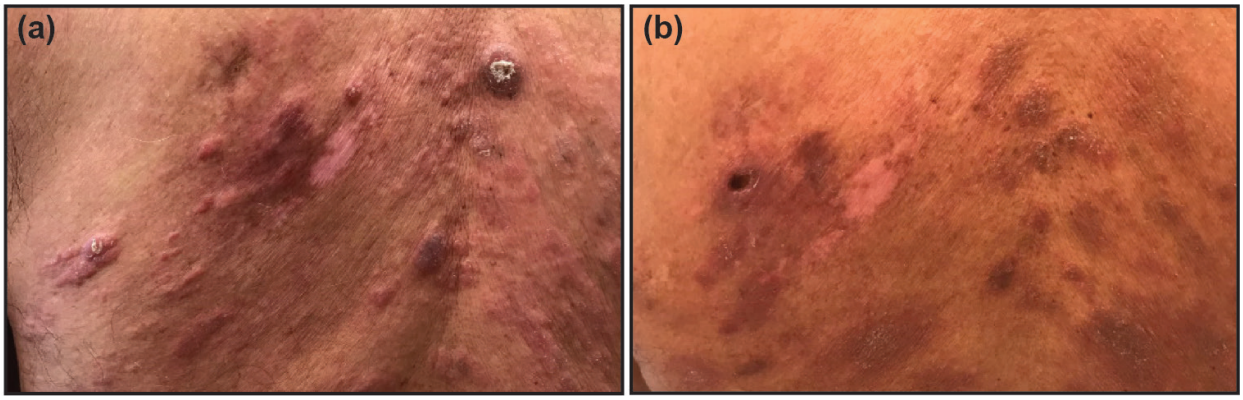

Figure 2. Clinical findings on the back of a patient with stage IIB MF. (**a**) Localized, thick persistent lesions before and (**b**) after treatment with intralesional rIFN-α2.

Table 1. The use of intralesional rIFN-α2 in the treatment of plaque-stage MF.

# of Patients	Dose/Duration	Stage	Response	Reference
9	2 MU (3x per week)	I	3 CR, 6 PR	Wolff *et al.* 1985 [3]
6	1 MU (3x per week)	I, II	10 lesions CR, 2 lesions PR	Vonderheid *et al.* 1987 [2]
3	1 MU	I, II	2 PR	Qiu *et al.* 1996 [4]
1	0.5 MU (3x per week) / 1 MU (3x per week)	I	CR	This report
1	0.5 MU (3x per week) / 1 MU (3x per week)	II	CR	This report

Key: CR (complete response), complete clinical remission (100% of lesions); PR (partial response), diminution of measurable disease (>0% lesion resolution, but <100%); SD (stable disease), no discernible change in lesions; PD (progressive disease), >50% worsening of skin lesions. Stage I: T1/T2, N0, M0, B0/B1; Stage II: T1/T2/T3, N0/N1,N2, M0, B0/B1.

resulting in resolution (Figure 2b).

DISCUSSION

The clonal T-cells of MF produce IL-4 and IL-5 with diminished local levels of IL-12, IFN-γ, and IFN-α, thereby creating a cytokine imbalance that is both pro-inflammatory as well as inhibitory to anti-tumor immunity [5,6]. Unregulated production of IL-10 and TGF-β seen in MF patients has also been hypothesized to diminish cell-mediated immunity, potentially contributing to the increased incidence of both infection and secondary cancers [5].

Directly, rIFN-α2 prevents tumorigenesis through the induction of cell cycle arrest, as well as both intrinsic and extrinsic apoptotic pathways [7]. Indirectly, the polypeptide inhibits angiogenesis, while modulating the immune antitumor response through the activation of cytotoxic T-cells and natural killer cells [8].

A glycoprotein rapidly degraded within the digestive tract, rIFN-α2 is administered intravenously, intramuscularly, or subcutaneously to achieve systemic levels. Intravenous rIFN-α2 has exhibited equivocal efficacy in MF stage IV patients and is less commonly utilized because of the rapid decline in serum concentration following administration [9]. Both intramuscular (IM) and subcutaneous (SC) administrations have demonstrated significant anti-tumor activity, resulting in partial or complete responses in MF patients at various stages of disease [9]. However, IM and SC delivery requires higher dosing for therapeutic efficacy, leading to considerable systemic toxicity and a constellation of dose-dependent side effects such as fevers, thrombocytopenia, leukopenia, and sepsis [9]. Studies with higher doses (>30 MU IFN/week) given through IM injections necessitated dose reductions in as high as 50% of patients because of significant toxicity [10].

In response to these limitations, rIFN-α2 has also been delivered intralesionally (Table 1). Requiring lower doses to achieve plaque regression, intralesional rIFN-α2 has been recommended as a more tolerable alternative [9]. The doses of intralesional injection in prior reports ranged from 1-2 MU 3x/wk, with response times that varied from 4-12 weeks [2-4]. Several cohort pilot studies also reported beneficial effects in uninjected plaques, with improvement in distant lesions in as many as 7 out of 9 patients treated with intralesional rIFN-α2 [3]. Whether the response represented an abscopal effect and/

or systemic immunostimulation is unclear. In one report, intralesional injection of rIFN-α2 reduced helper T-cell/suppressor T-cell ratios within treated lesions [3]. Moreover, three patients who had previously failed IM rIFN-α2 therapy experienced complete resolution of their lesions after initiating intralesional rIFN-α2 [4]. Although the incidence and severity of side effects were lower than those observed with high dose IM or SC injections, patients still experienced transient flu-like symptoms [2].

Our patients were initiated with 0.5 MU injections 3x/wk, resulting in substantial responses in injected lesions in the notable absence of systemic side effects. This experience suggests that initiation of intralesional rIFN-α2 at 0.5 MU per injection 3x/wk may be a well-tolerated therapeutic strategy in the management of MF.

CONCLUSION

MF is a cutaneous malignancy characterized by its chronic course and high rate of recurrence, thus presenting a significant challenge for therapeutic management. Our experience suggests that intralesional injections of rIFN-α2 at doses as low as 0.5 MU 3x/wk may be efficacious, and used safely in patients receiving other skin-directed and systemic therapies. Although further controlled, large-scale studies are required to investigate the efficacy of intralesional IFN, low-dose intralesional IFN may offer a well-tolerated option in the local immunotherapy of early-stage MF.

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