

THERAPEUTIC HOTLINE: SHORT PAPER

Relief of intractable pruritus with romidepsin in patients with cutaneous T-cell lymphoma: A series of four cases

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Abstract

Cutaneous T-cell lymphomas (CTCL) are a relatively rare and heterogeneous group of non-Hodgkin lymphomas that typically present in the skin. The majority of patients with CTCL experience pruritus, which can interfere with daily activities, significantly impact quality of life, and is typically uncontrolled by standard anti-itch therapies. Several lymphoma treatments have reported anti-pruritic effects including romidepsin, a potent class 1 selective histone deacetylase inhibitor approved for the treatment of patients with CTCL who have had at least one prior systemic therapy. Here, we describe the cases of four patients with debilitating and refractory pruritus that were resolved with romidepsin. Resolution of pruritus was observed in both clinical responders and nonresponders, and dose modification was used successfully to manage adverse events and for maintenance treatment. The potential for pruritus relief with romidepsin should be considered when treating patients with CTCL.

KEYWORDS

cutaneous T-cell lymphoma, lenalidomide, pruritus, romidepsin

1 | INTRODUCTION

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of non-Hodgkin lymphomas characterized by skin-homing malignant lymphocytes (Ahern, Gilmore, & Poligone, 2012; NCCN, 2018). Patients typically present with cutaneous lesions, but extracutaneous sites (blood, lymph nodes, viscera) may be involved in advanced disease (NCCN, 2018). Most patients with CTCL experience localized or generalized pruritus, which can be debilitating and severely impact quality of life (Poligone & Querfeld, 2015). Standard anti-itch treatments (eg, antihistamines) are usually inadequate for treating CTCL-related pruritus (Ahern et al., 2012).

Romidepsin is a potent histone deacetylase inhibitor approved for patients with CTCL following ≥ 1 prior systemic therapy (Istodax [romidepsin] prescribing information, July, 2016). Here we describe four patients with intractable, debilitating, CTCL-related pruritus relieved by treatment with romidepsin.

1.1 | Case 1

A 64-year-old woman was diagnosed in 2009 with mycosis fungoides (MF) stage IB (body surface area [BSA] \approx 20–50%) by her primary

dermatologist and had received various topical steroids for 2 years and then topical nitrogen mustard (TNM) for 1 year without sufficient effect and continued significant pruritus. Her itch intensity, measured by visual analog scale (VAS) on a scale from 0 (no itch) to 10 (worst itch imaginable), was 9 to 10 (BSA, 30–60%). Interferon alpha-2b was started and discontinued after 1 month due to severe flu-like symptoms. Oral bexarotene resulted in stable disease for >6 months but without resolution of itch (VAS, 9 and 10; BSA, 60–70%). Sequential methotrexate, topical steroids, and a different compounding of TNM resulted in minimal improvement.

At 4 years post-diagnosis, the patient (remaining as stage IB) was started on intravenous romidepsin 14 mg/m² once weekly for 3 weeks of a 4-week cycle (qw 3/4) for 6 cycles. Although she experienced nausea and mild dysgeusia, there was no change in body weight or her normal diet. Her plaques were stable, but she described a dramatic improvement in itch. Within 1 month, VAS decreased to 6 (BSA, 60%); over the next 7 months, VAS decreased to 2 or 3 (BSA, 50–60%). Due to travel, she remained off all therapy other than occasional topical steroids for 6 months; during this time, VAS was 1. She underwent total skin electron beam (TSEB) therapy, resulting in clearance of skin disease for 2 months, and then recurrence, with itch remaining at VAS

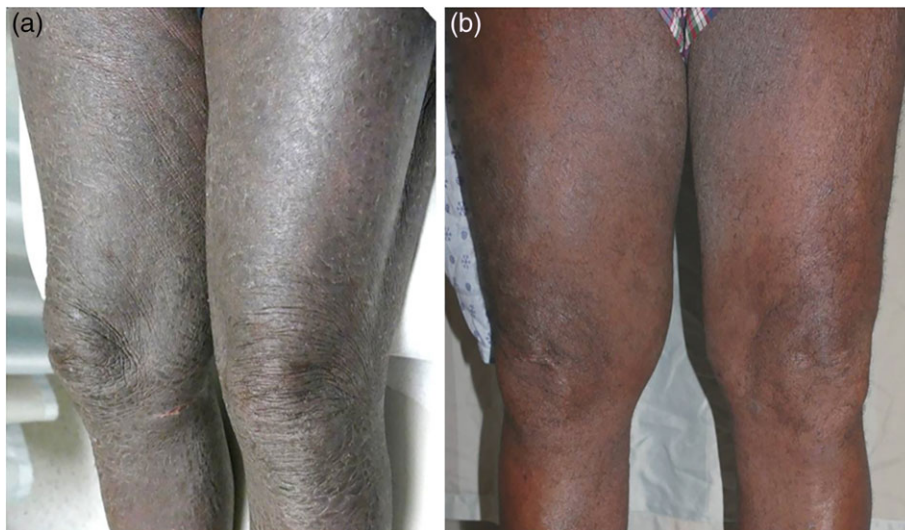


FIGURE 1 Cutaneous T-cell lymphoma. Case 3: Clinical response to romidepsin. Lower extremities before (a) and after (b) 4 cycles of romidepsin

0–1. In the intervening 6 months, she has remained off all therapies with stable disease (BSA, > 50%) and VAS of 0.

1.2 | Case 2

A 40-year-old woman presented with a severely pruritic, generalized rash that started 5 years ago. She was diagnosed with Sézary syndrome (SS) in 2011 with erythroderma, axillary and inguinal lymphadenopathy, and Sézary cell count of 5,000/ μ L. Multiple regimens failed, including bexarotene, gemcitabine, liposomal doxorubicin, brentuximab vedotin, and TSEB. Oral antihistamines and topical steroids did not improve her pruritus. She reported fatigue and weight loss. A skin biopsy was consistent with plaque-stage MF. CD4:CD8 ratio was >10:1, and a T-cell receptor (TCR) clone was identified in the blood, skin, and bone marrow.

She was started on romidepsin 14 mg/m² qw 3/4 combined with oral off-label use of lenalidomide 15 mg/day at a CTCL treatment center of excellence. She experienced nausea, vomiting, heartburn, and

loss of energy and appetite, which were manageable with supportive measures. She is currently on cycle 7 of treatment and is improving, with peripheral lymph nodes decreasing in size, partial clearing of skin lesions, and reduced pruritus for 7 months. At last visit Sézary cell count was negative. Pruritus improved significantly, was mostly localized, and did not require anti-itch medication on a regular basis.

1.3 | Case 3

A 57-year-old man with stage IVA2 SS presented with erythroderma in 2010, with onset over the past 6 months. A skin biopsy showed MF. CD4:CD8 ratio was 20:1, and a TCR clone was identified. The patient complained of severe itch at various visits (VAS, 5–10) and had prior treatment with topical steroids, gabapentin, doxepin, mirtazapine, extracorporeal photopheresis, interferon-alpha, and bexarotene. Treatment with vorinostat resulted in significant improvement in itch (VAS decreased from 9 to 5), but was discontinued due to significant diarrhea.

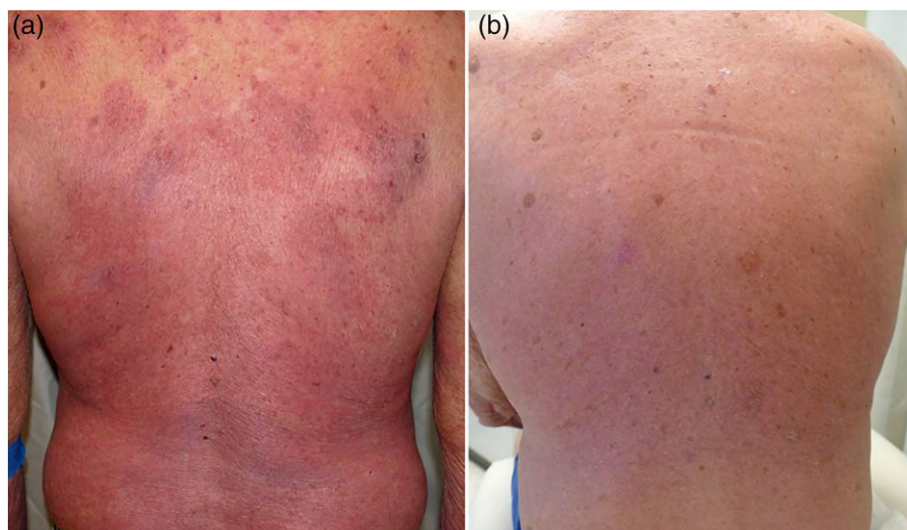


FIGURE 2 Cutaneous T-cell lymphoma. Case 4: Clinical response to romidepsin. The patient before (a) and after (b) 3 cycles of romidepsin. The patient presents less erythema and infiltration of most of the plaques and patches on his back after treatment

One month after discontinuation off all therapy, he had worsening itch (VAS, 7) and a high CD4:CD8 ratio of >10:1 by flow cytometry.

Two years after his initial diagnosis, the patient was started on romidepsin 14 mg/m² qw 3/4 for worsening of disease and pruritus. He had dramatic reduction of CD4:CD8 to 2:1 at 6 months, improvement in itch (VAS, 3), and resolution of erythroderma (Figure 1). Because of significant nausea, vomiting, and severe dysgeusia often lasting 3 or 4 days after infusion, romidepsin was reduced to 10 mg/m². At 12 months, the CD4:CD8 ratio was 2:1, no TCR clone was observed in the blood, and VAS was 1. Romidepsin was changed to 10 mg/m² every other week and occasionally once monthly. Blood was TCR negative at 18 months, and itch was reported to have been gone "for the past year." Romidepsin was discontinued at month 19 due to ongoing nausea and dysgeusia. He remained disease free for 12 months afterward. At month 14, a skin biopsy showed MF. Romidepsin was restarted at 14 mg/m² qw 3/4. Over 2 months, there was a partial response in the blood and itch did not recur. The patient underwent a bone marrow transplant and romidepsin was discontinued.

1.4 | Case 4

A 67-year-old man presented for evaluation of erythrodermic CTCL with gradually worsening erythroderma, lymphadenopathy, and recalcitrant pruritus. He noticed increasing scaling and thickening of skin with loss of hair on scalp and face. The patient had a history of atopic dermatitis since childhood. In 1979, he was diagnosed with psoriasis and has had erythroderma for >25 years. Numerous therapies failed, including topical steroids of various strengths, cyclosporine, and multiple clinical trials, including a TNF inhibitor, and an oral JAK 1/2 inhibitor for presumed psoriasis. He reported severe pruritus unresponsive to antihistamines. Sézary cell count was 4,607/μL, and a TCR clone was identified in the skin and blood. He was diagnosed with stage IVA SS.

He is currently on cycle 12 of romidepsin 14 mg/m² qw 3/4. He initially developed mild thrombocytopenia, which resolved. Fatigue, mild gastrointestinal symptoms (upset stomach, nausea), and loss of appetite usually resolved within 2 to 4 days. His skin is less thickened with minimal erythema (Figure 2); hyperkeratotic plaques on the soles and hands resolved, with only focal fine fissuring on palms noted; peripheral lymphadenopathy decreased in size. At last visit, Sézary cell count was negative; he is in partial to near complete remission. His pruritus improved significantly, with one mild flare per week, mostly localized, without need for anti-itch medication.

2 | DISCUSSION

While the mechanism behind CTCL-related pruritus remains unclear, abnormally high expression of type 2 helper T-cell (Th2) cytokines including interleukin [IL]-4, IL-5, IL-13 which trigger eosinophilia and elevated immunoglobulin E production (Ahern et al., 2012; Suga et al., 2013), and IL-31, which has been correlated with pruritus severity in patients with CTCL (Nattkemper et al., 2016), have been implicated. Romidepsin may disrupt malignant Th2 cytokine release via an apoptotic- and/or epigenetic-modifying pathway (Cedeno-Laurent et al., 2015; Singer et al., 2013), and lenalidomide through its immunomodulatory effects on

NK- and T-cells and the tumor microenvironment (Kotla et al., 2009; Querfeld et al., 2014). Here, debilitating and refractory CTCL-related pruritus in four patients was relieved by romidepsin alone or in combination with lenalidomide. Clinically meaningful reductions in pruritus in patients with CTCL have been documented in both romidepsin-responders and nonresponders (Kim et al., 2013), as was observed in one of our patients. Additionally, dose modification was used successfully to manage adverse events and for maintenance treatment. The clinical benefits of romidepsin, including the potential for pruritic relief, should be considered when treating patients with CTCL.

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CONFLICT OF INTEREST

B. Poligone: consultant and speaker: Celgene Corporation; B. Rubio-Gonzalez: nothing to disclose; CQ: honorarium: Celgene Corporation. Clinical Scholar: Leukemia Lymphoma Society (LLS); Clinical Investigator: Celgene, MiRagen, Trillium, Bioniz, Kyowa, Actelion; Advisory board: MiRagen, Bioniz, Trillium, Kyowa, Actelion.

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