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REVIEW

Pruritus Reduction with Systemic Anti-lymphoma Treatments in Patients with Cutaneous T Cell Lymphoma: A Narrative Review

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ABSTRACT

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous and relatively rare group of non-Hodgkin lymphomas arising from neoplastic skin-homing memory T cells. There is no known cure for CTCL, and current treatments focus on achieving and maintaining remission, controlling symptoms, limiting toxicities and maintaining or improving quality of life. Patients with CTCL often suffer from pruritus (itching), which can be debilitating and can have a significant impact on physical well-being and quality of life. Although progress has been made towards understanding the mechanisms of pruritus, the pathophysiology of CTCL-related pruritus remains unclear. Currently, there is neither a step-wise treatment algorithm for CTCL nor a standardized approach to treating pruritus in patients with CTCL. Treatments which specifically target pruritus have been reported with varying effectiveness. However, systemic treatments that target CTCL have the potential to alleviate pruritus by treating the underlying disease. Several systemic CTCL treatments have reported anti-pruritic properties, some in both objective responders and nonresponders, but the lack of a standardized method to measure and report pruritus makes it difficult to compare the effectiveness of systemic treatments. In this review, we provide an overview of approved and investigational systemic CTCL treatments that report anti-pruritic properties. For each study, the methods used to measure and report pruritus, as well as the study design are examined so that the clinical benefits of each systemic treatment can be more readily evaluated.

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Keywords: Cutaneous T-cell lymphoma; Itch; Pruritus; Therapy

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OVERVIEW OF CUTANEOUS T-CELL LYMPHOMA AND THE BURDEN OF PRURITUS

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of relatively rare lymphomas that comprise ≈4% of non-Hodgkin lymphoma cases diagnosed in the United States [1, 2]. CTCLs are caused by malignant helper T-cells that express a memory phenotype and localize to the skin [3, 4]. Mycosis fungoides (MF) and its leukemic variant Sézary syndrome (SS) are the most common forms of CTCL [2, 5]. Patients with CTCL typically present with erythematous patches in sun-protected areas, although visible changes to the skin can include any combination of patches, plaques, papules, tumours, and/or erythroderma [6, 7]. Correct, timely diagnosis of CTCL can be difficult because the clinical presentation and histology can resemble more benign conditions (e.g., eczema, psoriasis, other inflammatory dermatoses) and patients may initially have skin improvement with treatments for these conditions [8–10].

Although CTCL arises in the skin, advanced stages are associated with systemic involvement (lymph nodes, blood, visceral organs), with markedly reduced survival in advanced disease [7, 11]. In addition to physical burdens of disease, CTCL can also have a significant impact on patient emotional, functional, and psychological well-being and negatively impact quality of life (QOL) [12]; QOL worsens with disease progression [13]. The majority of patients with CTCL experience pruritus (itching), [12–15] often as the first symptom of disease [6]. Pruritus has been demonstrated to negatively impact patient QOL [12, 13]. For example, pruritus can interfere with sleeping patterns and impede daily activities, and patients with prolonged symptoms may require treatment for depression and insomnia [16]. Patients can experience severe pruritus regardless of disease stage, [13] although the incidence and severity of pruritus often worsens as the disease progresses [14]. In advanced CTCL, patients also commonly experience "burning pain" and sharp "pins and needles" [17]. The incidence and severity of pruritus are more pronounced with certain subsets of CTCL. Sézary syndrome is typically associated with severe pruritus, as well as generalized erythroderma and blood involvement with or without lymphadenopathy [10]. In a retrospective analysis of patients with CTCL ($N = 551$), 94% of patients with SS experienced pruritus compared with 61% with MF [14] and the mean pruritus score on a 10-point scale was 7.7 vs 3.6 for patients with SS and MF, respectively ($P < 0.001$). Folliculotropic MF is an aggressive variant of MF also associated with significant pruritus [10, 15, 18].

Currently, pruritus intensity is most often measured via a patient-reported visual analog scale (VAS) [19]. The VAS was first developed as a system to rate employees and has been subsequently adapted to measure pain, feelings, and other subjective criteria that cannot be directly measured or assessed by an external evaluator [13, 20–24]. For the VAS, the patient is given a line of fixed length where the end points are labelled and described (e.g., "no itching" to "unbearable itching") [22, 25]. Patients are instructed to mark on the line corresponding to their perceived state of itching.

Current CTCL treatments are focused on inducing and maintaining remission, controlling symptoms, limiting toxicities, and maintaining patient QOL [26, 27]. Given the impact of pruritus on patient QOL and the potential link to reduction in disease,

treatments that alleviate pruritus can provide a significant clinical benefit for patients with CTCL.

MECHANISMS OF PRURITUS IN PATIENTS WITH CTCL

Considerable advances towards understanding the mechanisms of pruritus have been described [28, 29]. However, the pathophysiology of CTCL-related pruritus remains unclear. Patients with CTCL may experience pruritus on skin lesions or uninvolved skin, even before other skin-related symptoms manifest [6, 16, 30]. These observations suggest that a soluble pruritic factor could be generated locally at the diseased skin or elsewhere in the body [16]. CTCL-related pruritus does not typically respond well to anti-histamine treatments, suggesting that mediators other than histamine may be involved [30, 31].

The cytokine expression profile of malignant T cells in CTCL is complex. A Th1-like profile has been observed in early-stage MF, while a Th2-like profile has been observed in later-stage MF and SS [32–34]. Recently, significantly higher levels of interleukin (IL)-31 have been found in patients with pruritic skin diseases compared to those without [35]. Reports have shown that patients with CTCL-related pruritus also had higher levels of IL-31 than those without and resolution of pruritus correlated with a decrease in IL-31 [36]. In another study, levels of IL-31 and severity of pruritus were correlated for patients with stage IB CTCL [30]. Interestingly, in vitro treatment of peripheral mononuclear blood cells (PBMCs) from patients with stage III-IV CTCL with vorinostat or dexamethasone suppressed production of IL-31. Treatment of patients ($n = 2$) with stage IV CTCL with a single dose of intravenous (IV) romidepsin resulted in suppressed production of IL-31 in PBMCs and a reduction in pruritus [37]. The majority of IL-31–producing T cells also express the skin-localizing receptor CC chemokine receptor 4 (CCR4), [37] and treatment of a patient with stage IV CTCL with the anti-CCR4 antibody mogamulizumab reduced pruritus and suppressed production of IL-31 in PBMCs [37].

The neuropeptide substance P, which is released from the ends of cutaneous sensory nerves, is an agonist of the neurokinin-1 receptor and has been implicated in itch [31, 38]. Use of aprepitant, which blocks the neurokinin-1 receptor, has been shown to relieve CTCL-related pruritus [39, 40]. Opioid receptors have also been implicated in pruritus [41]. Naloxone, an opioid receptor antagonist, has been found to reduce pruritus in patients with MF [42]; naltrexone, which also antagonizes opioid receptors, has been used with mixed results in patients with MF [6, 42]. Also, the proteinase-activated receptor 2 is located on cutaneous sensory neurons and has been found to mediate pruritus in atopic dermatitis, [43] which favours a Th2 cytokine profile similar to that of late-stage MF/SS [44].

Although central and peripheral-acting mediators have been proposed, the exact mechanisms of CTCL-related pruritus remain unclear, and further understanding of the pathophysiology of CTCL-related pruritus may provide new avenues for treatment.

CLINICAL STUDIES OF SYSTEMIC ANTI-LYMPHOMA AGENTS, INCLUDING ASSESSMENTS OF PRURITUS

National comprehensive cancer network (NCCN) guidelines recommend several topical

and systemic anti-pruritic treatments for CTCL-related pruritus [45]. However, as CTCL-related pruritus is ultimately a result of the lymphoma, controlling the disease may be an effective way to manage itch. Skin-directed phototherapies [psoralen and ultraviolet A (PUVA) and ultraviolet B (UVB)] have demonstrated the ability to induce remissions in early-stage disease, but few data are available regarding reduction of CTCL-related pruritus [45, 46]. In several case studies, treatment with PUVA resulted in improvement of pruritus in patients with Sézary syndrome [47, 48]. The effect of narrowband UVB on reduction of pruritus has been reported, but limited data are available in the context of CTCL [49, 50]. Other topical anti-lymphoma treatments such as carmustine, retinoids, and mechlorethamine (nitrogen mustard) have demonstrated effectiveness in inducing objective responses in early-stage MF, but may induce skin-directed adverse events that exacerbate pruritus rather than relieve it [5, 31, 51, 52]. Interestingly, a case series of 11 patients with CTCL treated with topical mechlorethamine resulted in the disappearance of pruritus [53]. A number of systemic anti-CTCL agents have documented anti-pruritic effects, but methods of pruritus assessment and data reporting vary across studies. In the following sections, we present studies of systemic anti-lymphoma agents, the method of pruritus assessment (if included), and the effects of each treatment on pruritus (Table 1). Inclusion of systemic anti-lymphoma agents in this narrative review was initially based on NCCN recommended agents. PubMed was searched for literature describing these recommended treatments with a focus on clinical trials which included assessments of pruritus. Additional papers were added to this initial literature through supplementary ad hoc searches.

This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Romidepsin

Class I selective histone deacetylase (HDAC) inhibitor [54] romidepsin (IV) is approved for patients with CTCL who have received ≥1 prior systemic therapy, [55] primarily based on results from a pivotal phase II study in patients ($N = 96$) with stage IB–IVA CTCL and ≥1 previous systemic treatment (a National Cancer Institute trial that supported the approval did not incorporate an assessment of pruritus) [22, 56, 57]. In the pivotal study, the majority of patients (60/65, 92%) with moderate to severe pruritus at baseline reported a reduction in their VAS score (mean change of −38 mm). Clinically meaningful reduction in pruritus (CMRP) was observed in 28/65 patients (43%) with moderate to severe pruritus at baseline—including 19/36 patients (53%) with severe pruritus at baseline. Seven patients with severe pruritus at baseline achieved complete resolution of pruritus for 2–8 months. Overall, the median time to CMRP was 1.8 months and the median duration of CMRP was 5.6 months. For patients with objective disease responses, 17/26 (65%) achieved CMRP, including 5/5 patients with complete response. However, CMRP also occurred in nonresponders (11/39, 28%)—all with best response of stable disease (SD). Patients were also able to achieve CMRP irrespective of disease compartment involvement; although lymphadenopathy significantly lowered rates of CMRP, erythroderma, blood involvement, and higher blood tumour burden (surrogate for SS) did not [58].

Table 1 Key parameters in studies of anti-CTCL treatments that included assessment of pruritus

Agent	Key trial details	Key efficacy data presented	Details of pruritus assessments provided	Use of anti-pruritic treatments on study
Romidepsin	Pivotal phase II study of patients ($N = 96$) with stage IB-IVA CTCL and ≥1 previous systemic treatment [22, 56]	ORR: 34% CR: 6% PR: 28% SD: 47% Median DOR: 15 mo	Patient-assessed 100-mm VAS; 0 mm = no itch to 100 mm = unbearable itching Moderate pruritus defined as VAS 30-69 mm; severe pruritus defined as 70–100 mm CMRP defined as a decrease in VAS of ≥30 mm for ≥2 consecutive cycles for patients with moderate to severe pruritus at baseline Complete resolution was described as VAS = 0 for 2 consecutive cycles	Concomitant anti-pruritic treatments not allowed
Bexarotene	Phase II/III study of patients ($N = 94$) with stage IIB-IVB CTCL refractory to ≥1 systemic anti-cancer therapy [62] Phase II/III study of patients ($N = 58$) with stage IA-IIA refractory CTCL or patients intolerant to or reaching a 6-mo plateau to prior treatment [63]	ORR: 45% (300-mg/m^2/day dose) ORR: 54% (300-mg/m^2/day dose)	Measured on a scale of 0–8 for up to 5 representative index lesions; 0 = none 2 = mild: less than average 4 = moderate: average 6 = severe: >25% worse than average 8 = very severe: near-worst severity Intermediate intervals of 1, 3, 5, 7 are to serve as midpoints between 0, 2, 4, 6, 8 Not stated whether the assessment was conducted with a VAS or verbally	Concomitant anti-pruritic treatments allowed
	Open-label phase II trial of doxorubicin HCl followed by bexarotene in patients ($N = 37$) with stage IB-IIA CTCL poorly responsive to skin-directed therapies or stage IIB-IV CTCL [64]	ORR: 41% CR: 6% PR: 35% SD: 18% Median PFS: 5 mo Median OS: 18 mo	Patient assessed 100-mm VAS, where 0 = no pruritus and 100 = worst imaginable pruritus Pruritus relief was defined as an improvement in pruritus ≥30 mm from baseline or complete resolution of symptoms	Concomitant use of topical corticosteroids was permitted for patients with intense pruritus

Table 1 continued

Agent	Key trial details	Key efficacy data presented	Details of pruritus assessments provided	Use of anti-pruritic treatments on study
	Open-label pilot study in combination with rosiglitazone for patients ($N = 4$) with stage IA-IVA CTCL with SD with or PR to single-agent bexarotene [65]	ORR: 25% CR: 0% PR: 25% SD: 75%	Patient assessed 100-mm VAS	No details for use of concurrent anti-pruritic provided
Denileukin diftitox	Placebo controlled phase III study of patients ($N = 144$) with stage IA–III CTCL, ≤3 prior therapies, CD25 positive on ≥20% of T cells in biopsied skin lesions [67]	ORR: 44% CR: 10% PR: 34% SD: 35% Median PFS: 26 mo for 9-μg/kg/d dose, NR for 18-μg/kg/d dose Median DOR: 8 mo	Patient assessed 100-mm VAS Details on how "clinically significant improvement" was defined were not included	Premedication with an anti-histamine was required 30–60 min before study drug administration and allowed during and after the dosing period
	Phase III study of patients ($N = 71$) with stage IB-III CTCL, ≥ 4 previous treatments, CD25 positive on ≥20% of T cells in biopsied skin lesions; patients with stage IVA disease could enrol if they had ≥1 previous therapies fail [68, 69]	ORR: 30% CR: 10% PR: 20% SD: 32% Median DOR: 7 mo	Patient assessed 100-mm VAS scale; 0 = no itch, 100 mm = worst imaginable itch Clinically significant baseline pruritus defined as ≥20 mm Significant improvement defined as improvement of ≥20 mm	Premedication with an anti-histamine 30–60 min before study drug administration and use of 25 mg promethazine or 10 mg proclorperazine for nausea allowed; use of pruritus rescue medication was allowed and recorded

Table 1 continued

Agent	Key trial details	Key efficacy data presented	Details of pruritus assessments provided	Use of anti-pruritic treatments on study
Vorinostat	Phase II study in patients ($N = 33$) with stage IA-IVB CTCL refractory or intolerant to conventional therapy [71]	ORR: 24% CR: 0% PR: 24% Median DOR: 4 mo	Patient assessed score from 0 to 10; VAS or verbal not specified Pruritus relief was defined as a reduction of ≥3 points or compete resolution for ≥4 wk Complete resolution was a score of 0 for ≥4 wk	Anti-histamines and topical steroids allowed if stable dose for ≥2 wk (changes/increases not allowed on study)
	Phase IIb study in patients ($N = 74$) with stage ≥IB CTCL and ≥2 prior systemic therapies, 1 of which had to be bexarotene unless it was not tolerated [72]	ORR: 30% CR: 1% PR: 29% Median DOR: NR; estimated to be at least 5 mo	Patient assessed VAS from 0 to 10; 0 = no pruritus to 10 = worst imaginable Severe pruritus defined as a score of 7–10 points Pruritus relief defined as ≥3-point reduction in patients with a VAS score of ≥3 points, or a complete resolution of pruritus for ≥4 continuous weeks without the use of anti-pruritic medications	Supportive treatment with anti-histamines allowed; patients on topical (all) and systemic steroids (Sézary syndrome) for ≥3 mo were allowed to continue
	Open-label, nonrandomized, escalating dose, phase I study, in combination with bexarotene, in patients ($N = 23$) with stage ≥ IB CTCL refractory to ≥1 prior systemic therapy (not including bexarotene) [73]	ORR: 17 CR: 0% PR: 17% SD: 65%	Patient assessed VAS of 0–10 Pruritus relief defined as reduction of ≥3 points from baseline or complete resolution	No details for use of concurrent anti-pruritic provided

Table 1 continued

Agent	Key trial details	Key efficacy data presented	Details of pruritus assessments provided	Use of anti-pruritic treatments on study
Alemtuzumab	Phase II study in patients ($N = 22$) with CD52+ stage II–IV MF/SS with ≤5 systemic treatments and not responding adequately to PUVA, radiotherapy, chemotherapy, or interferon alpha [74]	ORR: 55% CR: 32% PR: 23% SD: 13% Median DOR: 12 mo	Patient assessed 100-mm point VAS, 0 indicates no itching; 100-mm indicates worse possible itching	Patients received anti-histamine 30 min before infusion until first dose reactions disappeared; use of corticosteroids during week 1 was optional
	Phase II study of patients ($N = 8$) with stage IIB–IV relapsed/refractory CTCL [75]	ORR: 38% CR: 0% PR: 38% SD: 25%	Self-assessment on a scale of 0–8; 0 = no itching to 8 = very severe itching Significant improvement defined as 50% improvement in self-assessment score	Promethazine and hydrocortisone allowed for infusion-related side effects
Extracorporeal photopheresis	Retrospective single center study of patients ($N = 55$) with stage III–IVB SS treated with ECP [76]	Good response: 62% PR: 18%	Method of pruritus assessment not detailed	No details for use of concurrent anti-pruritic provided
Zanolimumab	Open-label phase II study of patients ($N = 47$) with refractory stage IB–IVB MF/SS [79]	ORR: 32%	Method of pruritus assessment not detailed	Topical steroids allowed as a rescue therapy for patients developing eczematous dermatitis not involving target lesions
Belinostat	Open-label phase II study of patients ($N = 29$) with relapsed/refractory stage IB–IVB CTCL who had ≥1 prior systemic therapies fail [80, 83]	ORR: 14% CR: 10% PR: 3% SD: 35% Median DOR: 3 mo	Pruritus assessed using a 10-point scale; VAS or verbal not specified Severe pruritus defined as score 7–10 Pruritus relief defined as reduction of pruritus score of ≥3 points in patients with baseline score ≥3	No details for use of concurrent anti-pruritic provided

Table 1 continued

Agent	Key trial details	Key efficacy data presented	Details of pruritus assessments provided	Use of anti-pruritic treatments on study
Panobinostat	Open-label phase II study of patients with previous exposure to bexarotene ($n = 79$) or bexarotene naive ($n = 60$) with stage IB-IVA MF or SS who had ≥2 prior systemic therapies fail [81]	ORR: 17% CR: 1% PR: 16% SD: 21% Median PFS: 4.6 for bexarotene exposed; 3.7 mo for bexarotene naive Median DOR: 9.2 mo for bexarotene exposed; NR for bexarotene naive	Patients completed assessments via VAS throughout the study Pruritus relief not defined	No details for use of concurrent anti-pruritic provided

CTCL cutaneous T-cell lymphoma, *ORR* overall response rate, *CR* complete response, *PR* partial response, *SD* stable disease, *DOR* duration of response, *mo* month, *VAS* visual analog scale, *CMRP* clinically meaningful reduction in pruritus, *PFS* progression-free survival; *OS* overall survival, *NR* not reached, *MF* mycosis fungoides, *SS* Sézary syndrome, *PUVA* psoralen + ultraviolet A, *ECP* extracorporeal photopheresis, *HCI* hydrochloride, *wk* weeks

In evaluable patients with folliculotropic disease involvement ($n = 9$), patients with moderate to severe pruritus at baseline had a mean reduction in VAS of −53 mm (−60 mm for those with severe pruritus) and 1 patient had complete resolution of pruritus [59]. In evaluable patients with cutaneous tumours ($n = 19$), patients with moderate to severe pruritus had a mean reduction in VAS of −43 mm (−45 mm for those with severe pruritus) and two patients had complete resolution of pruritus [59]. In evaluable patients who received prior systemic chemotherapy ($n = 50$), 24 (48%) experienced CMRP [60].

Bexarotene

Retinoid bexarotene (oral) is approved for the treatment of cutaneous manifestations in patients with CTCL refractory to ≥1 prior systemic therapy [61]. In a phase II/III study in patients ($N = 94$) with stage IIB-IVB CTCL refractory to ≥1 systemic anti-cancer therapy, the mean pruritus score at baseline was reduced at week 48 regardless of concomitant antihistamine/antipruritic treatment [62]. In a phase II/III study of patients ($N = 58$) with stage IA-IIA refractory CTCL (or who were intolerant to or reaching a 6-month plateau to prior treatment), pruritus for representative index lesions decreased from mild-moderate at baseline to mild-absent by week 16 [63]. Pruritus continued to improve independent of additional anti-histamine and/or anti-pruritic use. Additionally, a phase II trial was conducted to examine doxorubicin hydrochloride (HCl) followed by bexarotene in patients ($N = 37$) with stage IB-IV CTCL (or stage IB-IIA disease poorly responsive to skin-directed therapies) [64]. Following treatment with doxorubicin HCl, 53% of patients had pruritus relief (5/9 responders; 3/6 patients with SD), and following subsequent bexarotene treatment, 71% of patients had pruritus relief (3/5 responders; 2/2 patients with SD). In a pilot study of bexarotene in combination with rosiglitazone in patients ($N = 4$) with stages IA-IVA CTCL with SD or partial response to single-agent bexarotene, pruritus was alleviated in 3 patients (75%) [65].

Denileukin Diftitox

Diphtheria toxin/IL-2 fusion protein denileukin diftitox (DD; IV) is approved for persistent or recurrent disease that expresses CD25 [66]; however, it is undergoing reformulation and has been withdrawn from the market [45]. In a phase III study of patients ($N = 144$) with CD25+ stage IA–III CTCL who had received ≤3 prior therapies, clinically significant improvement in pruritus was reported in 9.1% of patients with placebo vs 13.3% with DD 9 μg/kg/days ($P = 0.7681$) and 34.5% with DD 18 μg/kg/days ($P = 0.0048$) [67]. In a separate phase III study of patients ($N = 71$) with CD25+ stage IB–III CTCL with ≥4 previous treatments (stage IVA allowed if they had ≥1 previous therapies fail), [68, 69] 53/71 of patients (75%) had significant pruritus at baseline, of whom 36 (68%) had a clinically significant improvement (decrease of ≥20 mm) [68]. All 17 responders and 13/23 patients (57%) with SD with clinically significant pruritus at baseline showed significant improvement [68]. The median decrease in pruritus was 22 mm in responders ($n = 21$; 50% decrease from median at baseline; $P < 0.05$) and 20 mm in nonresponders ($n = 45$; 6% decrease from median at baseline) [69].

Vorinostat

Pan-HDAC inhibitor [54] vorinostat (oral) is approved for patients with CTCL with progressive, persistent, or recurrent disease on or following two systemic therapies [70]. In the initial phase II study in patients ($N = 33$) with stage IA–IVB CTCL refractory or intolerant to conventional therapy, 31 patients had a baseline pruritus score [median of 8 (range 0–10)] and 14 patients (45%) experienced pruritus relief, 3 of whom had complete resolution of pruritus [71]. Among patients with baseline pruritus scores of 3–6 and 7–10, 33% and 59% experienced relief, respectively, typically within 4 weeks of study start. The overall mean reduction in pruritus score was 3, and patients with SS who did not achieve objective responses were able to achieve pruritus relief. In a phase IIb study in patients ($N = 74$) with stage ≥IB CTCL and ≥2 prior systemic therapies (1 of which must be bexarotene unless not tolerated), 21/65 patients (32%) with a baseline pruritus score ≥3 experienced pruritus relief [72]. Of 30 patients with a baseline score 7–10, 13 (43%) experienced pruritus relief, including 5/16 patients with SS; 30% achieved a score <3 at 2 or more consecutive visits. Of 21 patients with an objective response, 10 (47%) experienced pruritus relief; 13/51 nonresponders (26%) experienced pruritus relief [72]. For patients with stage ≥IIB disease, median time to and duration of pruritus relief was 16 days and 3.7 months, respectively. In a phase I study of vorinostat in combination with bexarotene in patients ($N = 23$) with stage ≥IB CTCL refractory to ≥1 prior systemic therapy (not including bexarotene), 7/23 patients (30%) experienced pruritus relief, including nonresponders [73].

Additional Agents

Anti-CD52 monoclonal antibody alemtuzumab (IV) is an agent included in recommendations for the treatment of stage ≥3 MF/SS with disease progressive or refractory to multiple prior therapies [45]. In a phase II study in patients ($N = 22$) with CD52+ stage II–IV MF/SS previously treated with ≤5 systemic treatments (and not responding adequately to PUVA, radiotherapy, chemotherapy, or interferon alpha), median VAS was 80 mm at baseline and 20 mm at treatment end in 17 evaluable patients [74]. Median VAS was 80 mm for objective responders ($n = 11$) and 60 mm for nonresponders ($n = 6$) at baseline and 10 and 50 mm, respectively, at treatment end. Three of six nonresponders had best VAS score reductions of ≥10 mm [74]. In a phase II study of patients ($N = 8$) with stage IIB-IV relapsed/refractory CTCL, four patients (50%) reported significant improvement in pruritus [75]. Extracorporeal photopheresis is a recommended treatment for MF/SS, particularly for patients with blood involvement [45]. In a retrospective single center study of patients ($N = 55$) with stage III–IVB SS, 37/44 (84%) responders had >50% improvement in pruritus [76]. Low-dose methotrexate is also included in NCCN recommendations, and has a history of being used to treat patients with CTCL [45, 77]. The impact of methotrexate on CTCL-related pruritus has not been well documented, but anecdotal information suggests the potential for pruritus reduction [6]. Case study data of patients treated with interferon-α also report a decrease in pruritus [78].

The remaining agents discussed are investigational and are not currently approved or recommended by the NCCN. In a phase II

study of the anti-CD4 monoclonal antibody zanolimumab (IV) in patients ($N = 47$) with refractory stage IB–IVB MF/SS, 11/13 responding patients (85%) and 13/25 nonresponders (52%) reported improvement in pruritus severity [79]. In a phase II study of the pan-HDAC inhibitor [54] belinostat (IV) in patients ($N = 29$) with relapsed/refractory stage IB–IVB CTCL who received ≥1 prior systemic therapy, [80] 7/15 patients with baseline pruritus ≥3 had pruritus relief, including 3/6 with severe pruritus at baseline [80]. In a phase II study of the pan-HDAC inhibitor [54] panobinostat (oral) in patients ($N = 139$) with stage IB-IVA MF or SS who have ≥2 prior systemic therapies fail, 24/97 patients (25%) with baseline pruritus greater than the standard deviation of the total group experienced pruritus relief [81].

SUMMARY AND RECOMMENDATIONS

Of all the anti-CTCL agents surveyed, HDAC inhibitors, romidepsin and vorinostat, have the most detailed published data on reduction of pruritus [22, 56, 71, 72]. Romidepsin and vorinostat studies used similar standards for pruritus assessment and analysed similar categories. Trials for romidepsin/vorinostat utilized a 100-mm/10-point patient-assessed VAS and defined significant pruritus reduction as ≥30 mm/3 points; only the romidepsin study required this for ≥2 consecutive cycles. The definition of complete resolution was more stringent in the study with romidepsin, requiring VAS = 0 for ≥8 vs ≥4 consecutive weeks [56, 71]. Subanalyses of the romidepsin study also showed that patients experienced pruritus reduction irrespective of disease compartment involvement, and in difficult-to-treat populations including patients with cutaneous tumours, folliculotropic MF, and those with prior chemotherapies [58–60]. Importantly, vorinostat trials allowed the use of concomitant anti-pruritic medications, which could impact results, whereas the romidepsin trial did not [56, 71, 72]. Although reported rates of significant pruritus reduction were similar for the two agents, this confounding factor must be considered. The durability of significant pruritus reduction was longer with romidepsin, even without concomitant anti-pruritic medications. Romidepsin has also been shown to produce durable clinical responses in patients with CTCL (median duration of response [DOR] 14–15 months) compared with vorinostat (median DOR 4–5+ mo) [56, 71, 72, 82].

New-generation HDAC inhibitor belinostat also used similar measures for pruritus assessments as romidepsin and vorinostat,[80] likely intentionally aligned due to precedent and for ease of comparison. Studies of single-agent bexarotene and DD also report detailed pruritus data; however, variations in assessments make comparisons with other agents difficult. Bexarotene studies used a 0–8 scale of ≤5 index lesions and did not define significant pruritus reduction [62, 63]. However, more recent combination studies did use a 100-mm VAS [64, 65]. DD studies used a 100-mm VAS [67–69]; however, when specified, the definition of significant reduction was less rigorous, at ≥20 mm [68]. Both bexarotene and DD studies allowed concomitant anti-pruritic medications [62, 63, 67–69].

While a review of literature demonstrates that pruritus reduction is recognized as an important aspect of treating CTCL, some studies of anti-lymphoma agents published in recent years include only a minimal analysis of pruritus [79–81]. None of the studies surveyed used pruritus as the primary endpoint, and

Table 2 ISCL, USCLC and Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer (EORTC) Consensus Recommendations for Pruritus Assessments in cutaneous T-cell lymphomas Clinical Studies [84]

Method for quantification	Severity of pruritus should be quantified using a VAS (number on scale not defined)
Definition of significant pruritus at baseline	Not defined, though recommendations assert the need to define
Definition of clinically significant change or threshold	Not defined, though recommendations assert the need to define
Comedications	Factors that could independently affect pruritus should be eliminated
	Any concomitant anti-pruritic agents should be at a stable dose or discontinued when making comparative pruritus measurements
	No claim of absence or resolution of pruritus should be made with concomitant use of anti-pruritic treatments
Appropriate terminology	General terms that imply complete resolution (e.g., "relief") should be avoided when referring to reduction or change in VAS
Relationship to disease response	Changes in pruritus should be correlated to disease response to put results in perspective

EORTC European Organisation for Research and Treatment of Cancer, *ISCL* International Society for Cutaneous Lymphoma, *USCLC* United States Cutaneous Lymphoma Consortium, *VAS* visual analog scale

existing pruritus data are difficult to compare across studies because the methods for assessing pruritus and reporting pruritus reduction are not standardized, although more recent studies more uniformly use a 100-mm/10-point VAS [64, 73, 80, 83]. Broad suggestions for assessment of pruritus have been published as part of a consensus statement on clinical endpoints and response criteria in CTCL (Table 2), but they lack definitive thresholds for clinical relevance [84].

Detailed recommendations regarding treatment selection based on pruritus reduction are difficult to make due to the nonstandardized ways in which pruritus data are gathered and presented across clinical trials of different agents. However, particularly for the approved agents, clinicians may consider initiating systemic treatment in patients with earlier stage disease who are struggling with pruritus. The impact of romidepsin on pruritus is well characterized, particularly because concomitant anti-pruritic treatments were not allowed during the studies, and romidepsin produces durable responses to treatment as well as durable pruritus reductions [22, 56]. Oral administration of vorinostat and bexarotene may be beneficial, particularly for early-stage patients who are not prepared for IV treatment. However, it is unclear whether the reported pruritus reductions are a result of the drug or concomitant anti-pruritic medications [62, 63, 71, 72]. This review provides a summary of what is currently known regarding the anti-pruritic properties of agents for the treatment of CTCL—both those approved and those in clinical development. While comparisons are difficult to make, it is clear that anti-lymphoma agents can reduce pruritus in patients with CTCL.

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