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REVIEW

Advances in the pharmacological management of cutaneous T-cell lymphoma

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ABSTRACT

Introduction: Current treatment guidelines for cutaneous T cell lymphoma (CTCL) advocate a stage-driven approach, considering clinical presentation, symptom burden, and patient comorbidities. Therapy selection hinges on factors like disease subtype, severity, and treatment availability. The primary goal is to enhance the quality of life by mitigating symptoms, as achieving lasting complete remission is infrequent.

Areas covered: Over the past decade (2013–2023), the therapeutic landscape of CTCL has experienced substantial transformation with the introduction of innovative therapies. This review explores the main pivotal developments in traditional treatment schedules and recently introduced drugs, aiming to offer clinicians and researchers a thorough perspective on the decade's progress in the field.

Expert opinion: Despite the progress made in CTCL therapeutics, ranging from topical chemotherapeutics to immunomodulatory agents, several unmet needs persist. Firstly, there is a pressing need for the incorporation of readily available predictors for treatment response, encompassing clinical, pathological, and molecular features. Secondly, a more profound comprehension of the tumor microenvironment is imperative to optimize the landscape of targetable molecules. Lastly, the undertaking of studies on combination regimens should be encouraged as it enhances therapy efficacies by synergistically combining agents with diverse modes of action.

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1. Introduction

Cutaneous T-cell lymphomas (CTCL) are a group of clinically heterogeneous T-cell lymphomas that arise in the skin [1]. The current international classifications delineate CTCL subtypes based on clinico-pathological characteristics, with Mycosis fungoides (MF) constituting around 40% and the leukemic variant Sézary syndrome (SS) around 2% of all cases [2,3]. As for these entities, accurate staging based on the TNMB staging system is pivotal for risk assessment, prognosis determination, and treatment planning [4]. Clinical presentations involving plaques and patches are classified as T1 (<10% body surface) or T2 (>10% body surface), whilst tumor stage and erythroderma define T3 and T4, respectively [1–5]. Lymph node (N) and visceral metastasis (M) involvements are assessed by imaging studies, whilst blood involvement (B) through flow cytometry on peripheral venous blood [1–3,6,7]. Stages IA, IB, IIA are defined as early-stage, whilst IIB, III and IV as advanced ones [8]. Treatment for all CTCL subtypes is based on an interdisciplinary approach involving dermatologists, hematologists, oncologists, and radiotherapists. The main objectives include symptom control and quality of life maintenance through tumor burden reduction [8]. Consensus statements by the EORTC support appropriate decision making in clinical practice. In 2017, a comprehensive study involving 853 retrospectively gathered patients from 21 global centers, conducted by the Cutaneous Lymphoma International Consortium (CLIC) in collaboration with the European Organization for Research and Treatment of Cancer (EORTC), the International Society for Cutaneous Lymphoma (ISCL), and the United Cutaneous Lymphoma Consortium (USCLC), unveiled substantial diversity in treatment approaches for advanced MF/SS. Notably, up to 24 different modalities or combinations were used as first-line, with 36% of patients receiving four or more treatments [9]. While significant variations in treatment modalities were observed between U.S.A. and non-U.S.A. centers, these differences did not correlate with survival. Chemotherapy as first treatment was associated with a higher risk of death and/or change of therapy, thus reinforcing the advisory against employing multiagent chemotherapy as the primary treatment, as established by a randomized trial in 1989 [10]. More recently, the establishment of the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) database in 2015 has emerged as a pivotal resource in collecting prospective data on MF patients [11,12]. In this context, a thorough analysis of early-stage MF patients emphasized the importance of disease characteristics such as plaques and folliculotropism in shaping treatment decisions, demonstrating the superiority of Skin-Directed Therapies (SDTs) over systemic therapy in such patients [11–13]. Traditionally, early-stage MF has been managed with first-line interventions such

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Article highlights

- Treatment for CTCL involves a multidisciplinary approach aiming at symptom control and maintaining quality of life.
- Skin-directed therapies include chlormethine gel alongside phototherapy, a historical treatment for early-stage MF, and radiation therapy, with low-dose TSEBT offering positive results.
- Systemic therapies feature Pegylated IFN-α 2a replacing older forms of IFN-α, retinoids demonstrating efficacy particularly in combination treatments, and chemotherapy-based regimens.
- Immunomodulatory agents like brentuximab vedotin, mogamulizumab, and lacutamab have reshaped the treatment landscape.
- Ongoing research focuses on new topical and systemic therapies, including PD-1/PD-L1 axis inhibitors and combination regimens.

as topical corticosteroids, phototherapy, and radiotherapy, occasionally adopting a 'wait-and-see' approach for minimally symptomatic patients [8,14]. For refractory or advanced cases, systemic agents, including immune modifiers, chemotherapeutic agents, and total skin irradiation, were considered [8,14]. Extracorporeal photopheresis (ECP) has long been employed for patients with erythrodermic and leukemic manifestations [8,14,15]. Maintenance treatments, utilizing either SDTs or systemic therapy, have been widely employed, particularly in advanced disease [8,14]. The past decade (2013–2023) has witnessed the introduction of new therapies that have significantly reshaped treatment strategies. This summary offers a comprehensive look at key advancements in both the schedules of traditional treatment regimens and recently introduced medications. Its objective is to provide clinicians and researchers with a renewed perspective on the progress made in the field over the last decade.

2. Skin-directed therapies

2.1. Chlormethine gel

The use of chlormethine, an alkylating agent with a history dating back to 1949, has been reported in uncontrolled studies for several decades [16]. In 2017 the European Medicines Agency approved the 0.02% gel formulation based on the results of the 201 randomized phase 2 trial, which demonstrated the non-inferiority of such compound compared to the ointment formulation in patients with stages I-IIA MF [17]. The response rates were 58.5% *versus* 47.7% (acc. Composite Assessment of Index Lesion Severity score, CAILS) and 46.9% *versus* 46.2% (acc. mSWAT score) for the gel and the ointment, respectively, with shorter time-to-response for the former. Therapy withdrawal due to skin irritation was recorded in 20.3% of patients in the gel treatment arm and 17.3% in the ointment treatment arm, though no evidence of systemic absorption nor increased skin cancers were detected during the 24-month observation period. Next, the open-label extension phase study 202 evaluated the efficacy and safety of chlormethine 0.04% in patients who did not achieve a complete response after the completion of 12 months of treatment, reaffirming the safety profile and providing evidence for the enhanced clinical benefits associated with the higher dosage and extended treatment duration [18]. Finally, within the PROVe study, the aim was to assess the impact of the topical drug in conjunction with additional therapies [19]. Following the prospective inclusion of 298 patients with stage IA-IB, 44.4% (treated with chlormethine + topical corticosteroids + other) and 45.1% (receiving chlormethine + other treatment) of participants achieved a favorable response after 12 months. Notably, a significant correlation emerged between responder status and lower post-baseline Skindex-29 scores [19]. In light of these findings, chlormethine gel is currently recommended as the first-line treatment for early-stage disease (stages IA to IIA) MF, with level II of evidence [8]. The suggested regimen involves applying the treatment once daily to affected areas, with the flexibility for whole-body surface application in cases of widespread disease. Given that contact dermatitis affects more than half of the patients, strategies to address this side effect have been developed and include interrupting treatment, extending intervals between applications, and combining with topical corticosteroids. Interestingly, post hoc analyses have hinted at contact dermatitis serving as an indicator for clinical response, which usually peaks after 10 months of therapy use [20,21]. The REACH study (NCT04218825) is seeking to unravel the origins of chlormethine-induced skin drug reactions and their connection to clinical responses [8].

2.2. Phototherapy

Phototherapy stands as a well-established treatment modality for early-stage MF, encompassing both narrow-band UV-B (nbUVB) and psoralen plus UV-A (PUVA). While nbUVB is typically employed for less infiltrated patch lesions, PUVA finds its utility in treating thick patches and plaques. However, existing literature has long grappled with variations in dosages, schedules, and indications for these approaches [8,14]. A recent meta-analysis has contributed valuable insights, revealing comparable overall response rates and adverse effect profiles between nbUVB and PUVA [22]. In 2021, an innovative Delphi consensus endeavored to establish standardized expert recommendations for phototherapy in MF treatment [23]. Predictably, the highest rates of agreement were achieved on queries relating to the traditional applications of phototherapy, such as early-stage MF, and matters pertaining to treatment schedules. Conversely, consensus on specific items was notably elusive as for the use of phototherapy for advanced-stage MF. This matter could be attributed to the scarcity of data in the literature and the limited experience in managing this less common subgroup. The consensus derived from the study underscored the pivotal role of phototherapy as the cornerstone of early-stage MF treatment, particularly for cases with extensive skin involvement or those exhibiting poor responsiveness to topical steroid therapy. While nbUVB is advocated as a monotherapy in most instances, consideration for PUVA and combinations with biologic response modifiers (such as retinoids and IFNs) is warranted when observing folliculotropism or inadequate response. Significantly, consensus was achieved on treatment schedules for both induction and consolidation phases, providing a standardized framework for guiding practitioners in optimizing the efficacy of phototherapy interventions [23].

2.3. Radiation therapy

Radiation therapy has represented a pivotal treatment modality for long time, offering both localized and total skin irradiation options. Traditionally, total skin irradiation involved a standard treatment course administering a total dose of 30–36 Gy over 8–10 weeks [8]. The 2015 pooled analysis of three clinical trials, employing a lower dose (12 Gy), revealed an overall response rate of 88% in patients with MF accompanied by a milder side effect profile [24]. Additionally, O'Malley *et al*. s research highlighted the effectiveness of radiation therapy by revealing substantial depletion of malignant T-cell clones at treated sites [25]. Remarkably, over 90% reduction in clonal presence was noted in the majority of treated lesions. Conversely, while topical corticosteroids yielded clinical enhancement, they showed persistent clonal activity, and the presence of residual malignant T cells was predictive of lesion recurrence. Furthermore, a retrospective analysis revealed that early-stage high-risk patients who underwent radiation as part of their treatment protocol experienced extended overall survival (OS) compared to those who did not. Likewise, administering a total skin irradiation of 8 Gy in 2 fractions has demonstrated effective disease management (ORR 89%, median TTNT 12 months) and symptom relief, while maintaining manageable toxicity levels [26]. When examining the duration of clinical benefit associated with conventional dose skin irradiation, prominent reports highlight significant challenges, especially among patients with poorer prognosis diseases such as SS and heavily pre-treated MF [27]. Notably, SS patients demonstrate a shorter TTNT, with a median of 3.7 months. Similarly, heavily pre-treated MF patients, particularly those who have undergone three or more prior treatments, experience a median TTNT of 7.1 months, contrasting with 23.2 months for patients with 0–2 prior treatments. These findings suggest a constrained role for conventional dose skin irradiation in SS cases, while indicating a potentially greater benefit when employed earlier in the treatment sequence for MF patients. Presently, the EORTC guidelines position TSEBT as a viable second-line therapy for early-stage MF and as a first-line option for cases classified as stage IIB-III MF, denoted as level 2 of evidence [8]. This endorsement underscores the advancing significance of low-dose TSEBT in the therapeutic arsenal for MF, as it shows high response rates, a favorable safety profile, and provides the flexibility of reirradiation during relapse or progression with reduced toxicities compared to the standard dose of TSEBT [8]. At last, the clinical advantage of low-dose TSEBT manifests in notable enhancements in terms of patients quality of life [28].

2.4. Pimecrolimus 1%

The efficacy and safety of topical pimecrolimus, a calcineurin inhibitor, was investigated in the single-arm, multicenter phase 2 trial PimTo-MF [29]. Conducted at six medical centers in Spain, the trial included patients aged ≥18 years with histologically confirmed early MF (stages IA-IIA) and an Eastern Cooperative Oncology Group performance status of 0–1. Exclusion criteria encompassed the concurrent use of treatments for MF, including sunbathing, corticosteroids, and other calcineurin inhibitors. Patients applied topical pimecrolimus 1% cream on skin lesions twice daily for 16 weeks (1 g per 2% of body surface), with a subsequent 12-month follow-up. The trial concluded the enrollment phase in September 2016 and comprised 39 patients with median follow-up of 5.7 years. The data published in 2022 reported overall response rates up to 56% (1 complete and 21 partial responses), spanning clinical stages IA (54% response) and IB (73% response) but not IIA. Topical pimecrolimus was well-tolerated, with no dose reductions or treatment discontinuations occurred due to drug-related toxicity. Adverse events were reported by 13 (33%) patients, with transitory mild burning or pruritus (grade 1) being the most common. The current EORTC guidelines caution that while the presented results show promise, their interpretation should be approached with care [8]. The efficacy and safety of pimecrolimus should ideally be confirmed through controlled trials with extended follow-up periods. Consequently, as of now, no specific recommendation regarding its use can be established.

2.5. Resiquimod

Published in 2015, the phase 1 trial by Rook *et al*. explored the efficacy of 0.03% and 0.06% topical resiquimod gel, a Toll-like receptor 7/8 agonist, in 12 patients with early-stage CTCL [30]. Notably, 75% of patients witnessed significant improvement in treated lesions, with 30% experiencing the clearing of all treated lesions. Moreover, the compound exhibited the ability to induce regression in untreated lesions. Significant improvement was reported also in cases of folliculotropic disease. Adverse effects were minimal and predominantly confined to the skin. The clinical improvement was coupled by a substantial decrease in clonal malignant T cells in 90% of patients, with complete eradication observed in 30%, and concomitant expansion of benign T cell clones. Overall, half of the patients displayed heightened activation of circulating dendritic cells, suggesting a systemic response to therapy. Despite these promising findings, topical Toll-like receptor agonists are not currently recommended in the international guidelines due to lack of solid data [8].

2.6. Tazarotene

In 2016, a Canadian open-label, prospective study explored the topical retinoid tazarotene as monotherapy for stages IA to IIA CTCL [31]. Over a period of 6 months on treatment, with an additional minimum of 6 months off treatment, index lesions in 10 patients were monitored. Notably, 60% of patients achieved a complete response (CR), with a progressive reduction in erythema, scaling, thickness, and lesion area throughout the treatment. The mean time to CR was 3.8 months, and CR proved to be durable for at least 6 months in 83% of cases. Among the remaining 40% without CR, 20% had stable disease, and 20% discontinued the medication due to local side effects, with none experiencing disease progression. Unfortunately, these promising results lacked follow-up, and the discontinuation of the product in Europe has hindered its use and inclusion as a treatment option in the recent guidelines [8].

2.7. Photodynamic therapy

In 2021, the first open-label trial investigating blue light photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) in refractory MF prospectively enrolled 11 patients having biopsy-confirmed refractory MF [32]. Refractoriness was defined as the failure of ≥ 2 skin-directed or ≥ 1 systemic therapy. Blue light ALA-PDT was administered every 4 weeks for a maximum of 6 cycles, employing four dose levels. The primary endpoints were Physician Global Assessment (PGA) and CAILS scores at 24 weeks. Objective response rates, as determined by PGA, CAILS, and modified CAILS, were 36.4%, 18.2%, and 36.4%, respectively, with no instances of complete remission or progressive disease. Adverse events were predominantly grade 1 or 2. Response rates exhibited an increase with ≥ 2 cycles, reaching a peak after 5 cycles. The study yielded essential insights into the efficacy and tolerability of ALA-PDT in refractory MF, suggesting potential benefits after 3 cycles. Overall, the less favorable outcomes and the limitation of PDT as a local treatment suitable only for specific skin areas underscore the necessity for future trials aimed at refining PDT-based protocols [8].

3. Systemic treatments

3.1. Interferon

Since receiving regulatory approval in the U.S.A. and Europe in 1986, IFN-α has found extensive application in CTCL therapy across various real-world settings. Emerging evidence over the past decade further supported its effectiveness. For instance, in a 2015 study comparing systemic therapies involving 198 patients, α-interferon showed a median TTNT of 8.7 months (95% CI 6.0–18.0), which was higher than single agent or multiagent chemotherapy (median TTNT 3.9 months) across all stages [33]. Moreover, the efficacy of combination regimens was examined in an open label clinical trial including 377 patients with refractory/relapsed CTCL randomly allocated to IFN-α + low-dose methotrexate or IFN-α + oral retinoid [34]. Notably, both groups attained an overall complete response rate of 80%, with comparable progression-free survival (PFS) rates (60% vs. 62%). These findings underscored the excellent tolerance and favorable outcomes exhibited by both treatment approaches. More recently, the discontinuation of previously available forms of recombinant IFN-α (IFN-α 2a, IFN-α 2b) from the market has led to a recommendation for their replacement with pegylated IFN-α 2a (peg-IFN-α 2a). While dose equivalence between pegylated and non-pegylated IFN-α is not established for efficacy or toxicity, the suggested starting dose is 135–180 µg/week administered subcutaneously [8]. In 2023, a German-Dutch retrospective experience involving 28 cutaneous T-cell lymphoma (CTCL) patients provided valid insight on the real-life effectiveness of Peg-IFN-α 2a [35]. Among these patients, only 7% opted for monotherapy, while the majority engaged in combination regimens, including PUVA (54%), local radiotherapy (29%), nbUVB (7%), chlormethine gel (25%), and topical steroids (32%). Despite an 18% overall incidence of side effects, discontinuation of Peg-IFN-α 2a occurred in only 2 patients due to hematological and gastrointestinal symptoms. Overall, the treatment resulted in 36% of patients achieving complete remission, 36% achieving partial remission, and 29% maintaining stable disease. These findings underscore the effectiveness of PEG-IFNα, particularly in combination with skin-directed therapies, especially in classic MF stages IIB and III [8,35].

3.2. Retinoids

Various retinoic acid receptor (RAR) agonists and retinoid X receptor (RXR) agonists have been used in the treatment of CTCL, with bexarotene being the sole on-label agent presently. The latest EORTC guideline does not provide conclusive evidence favoring one retinoid over another [8]. A recent study on TTNT indicates that both bexarotene and acitretin show good response rates (ranging from 66.6% to 75%) and therapy durations (median TTNT 9.8–14.5 months), with the former more frequently prescribed for more advanced patients (stage IIB), whereas acitretin for less advanced disease [36]. In the Japanese experience from post-marketing surveillance, a significant difference in objective response rates was observed between patients initiating bexarotene at 300 mg/m^2 and those starting with lower doses [37]. Therefore, commencing bexarotene at the prescribed dose of 300 mg/m^2 is currently recommended. Regarding acitretin, positive results have been reported in case of folliculotropic forms (ORR up to 72%) and early-stage disease (ORR up to 77.3%), despite no standardization in terms of schedule nor dosing [38,39]. Overall, retinoid monotherapy yields only moderate response rates, leading to their frequent use in combination or as maintenance therapy. Notably, a recent prospective study with 46 MF/SS patients demonstrated that pairing total skin electron beam therapy (TSEBT) with bexarotene notably boosted the response rate to 96%, compared to 68% with TSEBT alone [40]. This combination also led to a significant enhancement in median PFS (17 months vs. 5 months). Crucially, the addition of bexarotene did not elevate radiation-related toxicities. These findings strongly imply that integrating TSEBT with oral bexarotene holds promise for enhancing response rates and PFS among MF or SS patients.

3.3. Chemotherapy

Since the 1970s, non-Hodgkin's lymphoma has been treated with conventional single-agent chemotherapy and the CHOP regimen (Cyclophosphamide-Hydroxydaunorubicin-Oncovin-Prednisone). Despite using multi-agent chemotherapy, data suggests no clear superiority in response rates and remission duration compared to mono-chemotherapy, even when accounting for more severe side effects [8]. As such, single agents are the preferred agents, with gemcitabine and liposomal doxorubicin represent the most used agents in this setting. As for the former, a German multicenter study revealed a 62% overall response rate and a 12-month median PFS in a cohort of 37 MF and 11 SS patients [41]. Similar data was reported in another Italian single-center study, reporting a 54.5% overall response rate and a 17-month median PFS in nine MF and 13 SS patients [42]. As for liposomal doxorubicin, a recent Spanish retrospective study of 36 patients included

patients with tumors, erythroderma, blood, and nodal involvement, with a promising overall response rate of 78%. Notably, skin lesions exhibited the highest responses (31% complete response, 42% partial response), showcasing the treatment's effectiveness [43]. Nodal involvement proved to be more challenging, with 73% of patients showing unresponsiveness. The study highlighted liposomal doxorubicin's favorable safety profile, emphasizing its effectiveness in diverse compartments while underscoring variations in response rates based on the specific manifestation. Regarding SS patients, aggregated findings from an international study encompassing 178 individuals affirmed the short-term advantages in sustaining clinical benefits among those undergoing chemotherapy-based regimens [44]. TTNT statistics spanned from 3.1 months (multiagent) to 4.3 months (single agent) across all treatment lines.

3.4. Mogamulizumab

The MAVORIC trial, a phase III randomized study, compared the efficacy of the anti-CCR4 antibody mogamulizumab *versus* histone deacetylase inhibitor vorinostat (400 mg daily) in patients with MF/SS stage IB to IV, who had previously received at least one systemic therapy [45]. Notably, the trial included SS patients while excluding those with large-cell transformation. A markedly longer PFS for the mogamulizumab arm (median 7.7 *vs* 3.1; $p < 0.0001$), along with a significantly higher response rate (28% *vs* 5%), was reported compared to the control arm. Mogamulizumab outweighed vorinostat in all disease compartments, such as skin (42% *vs* 16%), blood (68% *vs* 19%), and lymph nodes (17% *vs* 4%). This advantage translated into enhanced symptom relief, improved functionality, and overall better quality of life, consistently favoring mogamulizumab over vorinostat at all evaluation time points [46]. Subsequent analysis revealed improved responses in patients with B1 or B2 scores in the blood, irrespective of clinical cutaneous stage [47]. Currently, research is advancing toward establishing combination therapies involving mogamulizumab and both skin-directed and systemic treatments. The MOGAT study, for instance, is exploring the combination of Mogamulizumab therapy with total skin electron beam therapy (TSEBT) (NCT04128072). In 2023, two studies by Weiner *et al*. and Ninosu *et al*. highlighted the potential benefits of Mogamulizumab in combination regimens [48,49]. Weiner *et al*.'s study included 19 patients (17 SS, 2 MF) with advanced-stage CTCL, achieving a global response in all cases, with 56% experiencing complete responses in a multimodality approach with systemic retinoids, interferon, or ECP [48]. Ninosu *et al*.'s retrospective study involving 11 patients with SS or MF demonstrated a 73% overall response in the skin, with an overall response rate of 64% in the blood, showcasing positive outcomes when combining mogamulizumab with ECP [49]. The most common adverse events included mogamulizumab-associated rash, anemia, lymphocytopenia, and infusion-related reactions. Importantly, no adverse event led to treatment discontinuation. It's noteworthy that the current literature extensively discusses the favorable prognostic impact of mogamulizumab-induced rashes [50]. Conversely, resistance to or evasion of mogamulizumab treatment has been linked to the emergence of CCR4- Sézary Cells in both blood and skin tissues [51]. Presently, mogamulizumab is recommended after failure of at least one prior systemic therapy, with a specific focus on stage III/IV MF/SS cases featuring significant blood involvement (i.e. B2), supported by level 2 of evidence [8].

3.5. Brentuximab vedotin

In 2017, the primary analysis of the ALCANZA trial revealed significant improvements in objective responses lasting ≥4 months (ORR4; primary endpoint) and PFS with brentuximab vedotin compared to physician's choice (methotrexate or bexarotene) in CD30-expressing mycosis fungoides (MF) or primary cutaneous anaplastic large-cell lymphoma (C-ALCL) [52]. Brentuximab vedotin not only enhanced skin symptom burden but also demonstrated no adverse effects on quality of life [52,53]. The publication of final data from ALCANZA in 2021 (median follow-up, 45.9 months) reinforced these findings [54]. The final data showcased superior responses with brentuximab vedotin compared to physician's choice: ORR4; 54.7% vs 12.5% ($p < 0.001$); complete response, 17.2% vs 1.6% ($p=0.002$). Median PFS with brentuximab vedotin vs physician's choice was 16.7 months vs 3.5 months ($p<0.001$). Additionally, the TTNT was significantly longer with brentuximab vedotin. Among patients experiencing any-grade peripheral neuropathy in the brentuximab vedotin arm, 86% achieved complete resolution or improvement. Ongoing peripheral neuropathy in 18 patients remained grades 1–2. These final analyses confirmed brentuximab vedotin's superiority, providing improved, clinically meaningful, durable responses and extended PFS in CD30-expressing MF or C-ALCL. An exploratory analysis further revealed brentuximab vedotin's efficacy in patients with CD30-positive MF and ≥ 1 biopsy showing ≥ 10% CD30 expression, irrespective of large-cell transformation status [55]. Of note, aggregate data on five prospective clinical studies in relapsed or refractory peripheral T-cell lymphoma, CTCL, or B-cell non-Hodgkin's lymphoma showed no significant differences in overall response nor duration of response between patients with CD30 expression ≥ 10% or < 10%, making the determination of a threshold level of expression uncertain [56]. Nevertheless, brentuximab vedotin is currently recommended as a first-line treatment for advanced stages after the failure of at least one prior systemic therapy, contingent on CD30 expression, and is supported by level 2 of evidence [8].

3.6. Allogeneic hematopoietic stem cell transplantation

The role of allogeneic hematopoietic stem cell transplantation (HSCT) has been the subject of diverse investigations in CTCLs through retrospective and limited prospective studies [8]. The potential induction of a graft-versus-lymphoma effect with allogeneic HSCT has been suggested to result in enduring disease remission in some patients [57]. However, more than half of the individuals experienced post-transplantation lymphoma relapse, with a 19% treatment-related mortality at two years [57]. A recent metanalysis spanning 2010 to 2023 showcased outcomes of HSCT for advanced-stage MF/SS [58]. Results included 1-year and 3-year OS of 51% and 40%, PFS

rates at 1 year and 3 years of 42% and 33%, and a 18% non-relapse mortality. Relapse occurred in 47%, with a median time of 7.9 months. Acute and chronic GVHD rates were recorded in 45% and 40% of cases. Reduced-intensity conditioning (RIC) yielded superior OS compared to myeloablative conditioning (MAC) (58% *vs* 30%) and 46% of relapsed patients achieved complete remission with donor lymphocyte infusion. In 2023, the results of the CUTALLO trial represented a further cornerstone in the therapeutic scenario of CTCLs [59]. This multicenter trial, spanning 30 hospitals, strategically assigned participants to allogeneic HSCT or non-HSCT therapy based on the presence of a compatible related donor. The inclusion criteria encompassed individuals aged 18–70 with advanced MF or SS and at least one poor prognostic criterion, excluding those not in complete or partial remission. Employing a 1:1 matching approach with replacement to counteract confounding factors, the primary endpoint of PFS in the matched intention-to-treat population was assessed (HSCT group $n = 55$, non-HSCT group $n = 44$). In the intention-to-treat analysis, HSCT significantly extended median PFS (9.0 *vs* 3.0 months, HR 0.38, $p < 0{\cdot}0001$); in the per-protocol population, 40 participants (78%) in the HSCT group experienced 101 serious events, while 29 participants (67%) in the non-HSCT group had 70 serious adverse events. In both groups, the most common serious adverse event, aside from graft-versus-host disease, was infections. The study suggests that individuals achieving pre-transplant disease remission, particularly those with high-risk MF or SS syndrome, may derive substantial benefit from allogeneic HSCT treatment. As outlined by the EORTC guidelines, the consideration for AlloSCT is recommended in patients with advanced disease and a poor prognosis, provided they lack significant comorbidities [8]. The guidelines underscore the importance of achieving complete or near-complete remission before opting for transplantation to optimize outcomes. Rather than being employed as a final option after exhausting all other treatments, AlloSCT is best suited for patients at a high risk of disease progression and mortality who have not yet become refractory to the most effective therapeutic options.

3.7. Lacutamab

In 2019, the phase-1 investigation of IPH4102 (lacutamab), a first-in-class monoclonal antibody targeting KIR3DL2, a cell surface protein expressed in CTCL and especially in SS, yielded promising results [60]. The study enrolled four patients, with 80% having SS, 18% MF, and 2% CTCL not otherwise specified. In the dose-escalation phase, no dose-limiting toxicity was reported, leading the safety committee to recommend a flat dose of 750 mg for cohort expansion, the maximum administered dose. Adverse events were predominantly grade 1–2, with peripheral edema (27%) and fatigue (20%) being the most common. Lymphopenia was the most frequent grade 3 or worse adverse event (7%). Unfortunately, one patient developed fulminant hepatitis after therapy discontinuation, leading to death, although evidence of human herpes virus-6B infection was present. The median follow-up was 14.1 months (IQR 11.3–20.5). A confirmed global overall response was achieved in 36.4% of patients, with 43% response in SS [60]. Subsequently, the multi-cohort phase 2 trial (TELLOMAK) aimed to confirm lacutamab's activity in Sézary syndrome and explore its role in other T-cell lymphoma subtypes expressing KIR3DL2 [60]. At the 64th ASH Annual Meeting in 2022, TELLOMAK data related to cohort 1 were presented, focusing on the safety and efficacy of single agent lacutamab in patients with relapsed/refractory SS after at least two prior systemic therapies, excluding those with evidence of large cell transformation [61]. Lacutamab (750 mg) was administered intravenously weekly for five weeks, every two weeks for ten cycles, then every four weeks until progression or unacceptable toxicity. Among the 37 patients who underwent treatment, with a median follow-up of 10.9 months, the predominant stage was IVA (94.6%), while 5.4% were at stage IVB. In the intention-to-treat population, the Global Confirmed Overall Response Rate (ORR) was 21.6%, with a confirmed ORR of 35.1% in the skin and 37.8% in the blood, including a 21.6% complete response (CR) as the best overall response. Notably, one of the 28 patients with lymph node involvement at baseline achieved a CR. Grade ≥ 3 Treatment-Related (TR) Treatment-Emergent Adverse Events (TEAEs) were observed in 16.2% of patients. Though currently not approved, these findings position lacutamab as a promising and prospective therapeutic option for the foreseeable future.

3.8. Anti-PD1/PDL1/CTLA4 agents

To date, few studies have explored the safety and efficacy of immune checkpoint inhibitors (ICIs) in the treatment of CTCLs. Two noteworthy trials have provided insights into this area. Lesokhin *et al*. conducted a phase I study with nivolumab, demonstrating good tolerability in 81 patients with hematologic malignancies, including MF and PTCL, with an overall response rate (ORR) of 15% in MF and 40% in PTCL [62]. Pembrolizumab was investigated in a phase II study involving 24 pre-treated MF and SS patients, showing an ORR of 38%, with two complete responses (CR) and seven partial responses (PR) [63]. Additionally, a phase 1b study explored pembrolizumab in combination with pralatrexate or decitabine, revealing promising responses, especially in the triple combination arm [64]. Genomic alterations of PD-L1 were investigated as potential biomarkers for PD-1 targeting therapy in CTCLs, providing valuable insights, yet requiring further exploration in larger studies [65]. Notably, the role of CTLA-4 inhibiting antibodies in CTCL remains uncertain, with limited data deriving mainly from case reports [66]. Overall, these findings underscore the necessity for further investigations to enhance our understanding and develop effective therapeutic strategies for CTCLs. The 2023 EORTC guidelines indicate that, based on the existing study results, no definitive conclusion regarding the clinical efficacy of anti-PD1/PD-L1 can be drawn [8]. It is advised to exercise caution when employing these agents in patients with T-cell malignancies outside of clinical trials. This caution stems from the unique nature of T-cell malignancies, where malignant tumor cells may simultaneously function as immunological effector cells [8,67].

3.9. Resminostat

HDAC inhibitors (HDACi) target epigenetic changes in CTCL and have been evaluated within the last decades, thanks to

their antitumor and anti-angiogenic properties [67,68]. From 2017–2022, the RESMAIN trial investigated the efficacy of Resminostat in a placebo-controlled phase 2b study [69]. In total, 201 patients with MF ($n = 164$) or SS ($n = 37$) have been enrolled and randomized to resminostat or placebo group. Treatment schedule involved oral intake on days 1–5 followed by a 9-day treatment-free period in 14 days circles. Resminostat showed beneficial effect on PFS versus placebo (median 8.3 vs 4.2 months) but failed to improve health related quality of life. So far, HDACi is not implemented in the latest update of the EORTC consensus recommendation as the official results are not published yet.

3.10. Antimicrobials

Topical and systemic antimicrobials are commonly employed in the context of CTCL. Notably, erythroderma in CTCL is linked to an increased prevalence of Staphylococcus aureus (S. aureus) [8]. A recent retrospective investigation at the MD Anderson Cancer Center scrutinized 26 erythrodermic CTCL patients, examining documented S. aureus colonization or infection events [70]. Treatment targeting S. aureus resulted in improvement in 53% of cases in terms of body surface area or mSWAT. The presence of methicillin-resistant S. aureus in 34% of events necessitated successful treatment with trimethoprim – sulfamethoxazole and doxycycline. Outpatients and individuals with prior anti-S. aureus decolonization treatments displayed lesser improvement in BSA or mSWAT. Similarly, a prospective study investigating CD4 T-cell responses to S. aureus revealed that aggressive, transient antibiotic treatment significantly mitigated clinical symptoms in 8 patients with advanced CTCL [71]. Sustained improvements were observed, accompanied by a reduction in malignant T-cell fractions in lesional skin, marked by the downregulation of CD25, STAT3 signaling, and cell proliferation. While these studies provide a compelling rationale for targeted S. aureus treatment in CTCL, the general level of evidence remains limited, and widespread treatment with antibiotics is not currently recommended [8].

4. Experts opinion

The exploration of therapeutic options for CTCL over the past decade has witnessed significant strides, reshaping the approach to treatment strategies. The diversity in CTCL subtypes, most notably MF and SS, necessitates an intricate understanding of disease characteristics for tailored interventions. Recent studies and real-life studies have not only shed light on novel molecules, ranging from chemotherapeutical topicals to immunomodulatory agents, but also reinforced the effectiveness of established treatment modalities. However, as we navigate through the evolving landscape of CTCL therapeutics, further research is imperative to furnish clinicians with accessible tools for delivering more personalized and tailored therapies to patients. The pressing need for such research lies in the scarcity of easily interpretable clinical, pathological, and molecular predictors of effectiveness in current practice [72]. Integrating relevant biomarkers such as CD30 for brentuximab vedotin, CCR4 for mogamulizumab, and KIR3DL2 for lacutamab, into advanced mutational panels via next-generation sequencing for emerging agents, offers potential advantages not only for clinical trials but also for their practical implementation in clinical settings [72]. Addressing this gap will not only enhance treatment precision but also contribute significantly to optimizing patient outcomes in the realm of CTCL, optimizing cost-effectiveness. While the PD-1/PD-L1/CTLA-4 immunotherapy axis has sparked a transformative era in melanoma treatment and is showing promising results in hematological T-cell malignancies, its application to CTCL seems constrained by intrinsic differences in the nature of these diseases [72–76]. Encouraging research has explored biomarkers' potential in guiding immunotherapy. For example, distinctive spatial patterns among effector PD-1+ CD4+ T cells, tumor cells, and immunosuppressive Tregs led to the development of the SpatialScore, strongly associated with pembrolizumab response in CTCL patients [77]. Another study suggests PD-L1 structural variants as potential genomic biomarkers for identifying CTCL patients responsive to anti-PD-1 immunotherapy, highlighting their role in treatment decision-making [65]. Nonetheless, CTCL's unique characteristics imply that the groundbreaking success seen in melanoma may not be easily replicated in this context. Instead, the prospects for promising outcomes in CTCL lie in exploring combination therapies with immunomodulating agents targeting other axes. Notably, agents like mogamulizumab and, hopefully soon, lacutamab hold greater promise. These combinations are anticipated to offer new avenues for therapeutic success in CTCL. In this regard, the commendable efforts of the MOGAT trial (NCT04128072), with its exploration of Mogamulizumab in conjunction with TSEBT, stand as a welcome initiative. This approach aligns with the understanding that synergistic immunomodulation could be the key to achieving significant advancements in the treatment landscape of CTCL. In essence, the road ahead demands sustained dedication to unravel the complexities of these malignancies. The collaborative efforts of clinicians, researchers, and the pharmaceutical industry, coupled with the resilience of patients, will pave the way for more effective, targeted, and personalized treatments, ultimately improving the outlook for individuals grappling with CTCLs.

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