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Systemic Treatment Options for Advanced-Stage Mycosis Fungoides and Sézary Syndrome

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Abstract

Purpose of Review Cutaneous T-cell lymphoma (CTCL) is a rare form of non-Hodgkin lymphoma. Globally, the most common subtypes of CTCL are mycosis fungoides and Sézary syndrome. CTCL can confer significant morbidity and even mortality in advanced disease. Here we review the current and potential future treatments for advanced-stage CTCL.

Recent findings Heterogeneity of treatment choice has been demonstrated both in US and non-US centers. Systemic treatment choice is currently guided by prognostic features, incorporating stage, immunophenotypic and molecular findings, and patient-specific factors such as age and comorbidities. Randomized controlled studies are uncommon, and the literature is composed predominantly of retrospective, cohort, and early-phase studies. International consensus guidelines are available; however, the lack of comparative trials means that there is no clear algorithmic approach to treatment.

Summary This review article reports on the systemic treatment options in current use for advanced CTCL, and on the possible future therapies, acknowledging that an algorithmic approach is not yet forthcoming to guide treatment prioritization.

Keywords Cutaneous T-cell lymphoma · Mycosis fungoides · Sézary syndrome · Bexarotene · Extracorporeal photopheresis · Interferon-alfa · Methotrexate · Brentuximab vedotin · Mogamulizumab · Allogeneic stem cell transplant · Vorinostat · Romidepsin · Denileukin diftitox · Doxorubicin · Gemcitabine · Pentostatin · Bendamustine · Monoclonal antibodies · Histone deacetylase inhibitors · Pralatrexate

Introduction

Cutaneous T-cell lymphomas (CTCL) comprise approximately 2% of all lymphomas, and are the result of the malignant transformation of skin-homing/resident T-cells [1]. Mycosis fungoides (MF) and Sézary syndrome (SS) account for the majority of CTCL presentations (54–72%), with an approximate incidence of 0.3–1.0 per 100,000 annually [1–3]. Due to its rarity and requirement for careful clinicopathological correlation, diagnosis of CTCL is frequently challenging and may be delayed. Best management should involve a multidisciplinary team, including dermatologists, hemato-oncologists, radiation oncologists, pathologists, specialist nurses, and clinical psychologists [4].

CTCL is primarily a disease of older adults, with a median age at diagnosis of 55–60 years, but may also occur in children and adolescents [1, 5]. The male-to-female ratio is 1.6–2.0:1 [1], with an apparent higher incidence in Africans and African-Americans [2]. The clinical stage is determined using the TNMB classification, first developed in 1979 [6] and recently revised [7] (Table 1). Stage determination is outlined in Table 2, incorporating physical examination, blood tests, skin biopsy, imaging, and lymph node biopsy when indicated [4]. Advanced stage is defined as the presence of tumors (T3/stage IIB), erythroderma (T4/stage III–IV), lymph node involvement (stage IVA), significant blood burden (stage IVA), or visceral metastases (stage IVB) [8].

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Table 1 ISCL/EORTC revision to the classification of MF and SS adapted from Olsen et al [7]

TNMB stages	Definition
SKIN	
T1	Limited patches, papules, and/or plaques covering < 10% of the skin surface 1. T1a—patch only covering < 10% of the skin surface area 2. T1b—plaque ± patch covering < 10% of the skin surface
T2	Patches, papules, or plaques covering > 10% of the skin surface 1. T2a—patch only covering > 10% of the skin surface 2. T2b—plaque ± patch covering > 10% of the skin surface
T3	One or more tumors (≥ 1 cm in diameter)
T4	Confluence of erythema covering ≥ 80% body surface area
NODE	
N0	No clinically abnormal peripheral lymph nodes; biopsy not required
N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade[a] 1 or NCILN (0–2)[b] 1. N1a—clone negative 2. N1b—clone positive
N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCILN (3) 1. N2a—clone negative 2. N2b—clone positive
N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 3–4 or NCILN (4); clone positive or negative
Nx	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells[c] 1. B0a—clone negative 2. B0b—clone positive
B1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2 1. B1a—clone negative 2. B1b—clone positive
B2	High blood tumor burden: ≥ 100/μl Sézary cells with positive clone

[a] Dutch grade developed by Scheffer et al. (1980) in Cancer 45: p.137–148. Based on features characteristic of dermatopathic lymphadenopathy, early involvement by MF, and partial or complete obliteration of the lymph node architecture by atypical lymphoreticular tissue, they devised a grading system of four categories to describe the histologic involvement of lymph nodes in MF

[b] NCI LN—National Cancer Institute Lymph Node classification system in CTCL as per Sausville et al. (1985) in Human Pathology 16(11): p. 1098–1109

[c] Sézary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. Large Sézary cells > 14 μm are specific to SS, but smaller cells may be present in 20–25% of patients with MF. A peripheral blood smear is used to count them. The ISCL in their consensus defined a Sézary cell count of 1 × 10(9) cells per liter as diagnostic of SS. If Sézary cells are not able to be used to determine tumor burden for B2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead: (1) expanded CD4+ or CD3+ cells with CD4/CD8 ratio of 10 or more, (2) expanded CD4+ cells with abnormal immunophenotype including loss of CD7 or CD26

Disease stage is critically important in determining prognosis and treatment strategies in CTCL patients. Seventy-one percent of MF patients have early-stage (I–IIA) disease at diagnosis and have a median survival of 12.9 years [9, 10]. Transformation to large cell lymphoma is uncommon in patients with early-stage disease (1.4%), but occurs in 25–30%

Table 2 Steps to determining stage in CTCL adapted from Olsen et al [7]

Steps to determine stage	
Complete physical examination	• Use the modified severity-weighted assessment tool (mSWAT) • If only patches/plaques: estimate the percentage of body surface area involved and note any ulceration • If tumors present: determine total number of lesions, aggregate volume, largest size, and regions involved • Identify any palpable lymph nodes • Identify any organomegaly
Blood tests	• CBC with differential, liver function tests, LDH, comprehensive chemistries • Flow cytometric assessment of Sézary cell count • Circulating T-cell subsets • Molecular testing via T-cell receptor gene rearrangement studies
Skin biopsy	• Take it from the most indurated area • Histology • Immunophenotyping • Molecular assessment for clonality of TCR gene rearrangement
Imaging	• In patients with early-stage disease, imaging can be limited to chest X-ray or ultrasound of peripheral nodal groups • In patients with more advanced or severe disease, positron emission tomography (PET)-computer tomography (CT) is recommended to evaluate potential lymph node and/or organ involvement
Lymph node biopsy as indicated	• Excisional biopsy is indicated in a node that is either ≥ 1.5 cm in diameter and/or is firm, irregular, clustered, or fixed • If multiple nodes, preference is given to the largest • If multiple and all large, then the order of preference is cervical, axillary, and inguinal areas • Analysis: light microscopy, flow cytometry, and TCR gene rearrangement

of patients with tumors; these patients tend to do poorly [11, 12]. Median survival in those with advanced stage at diagnosis is 4.0 years for stage IIB/III, and 1.5 years for stage IV [9].

SS classically presents with erythroderma, generalized lymphadenopathy, and peripheral blood involvement with Sézary cells, and is, by definition, advanced disease, with a median survival of less than 3 years [10, 13]. Indeed, the pathobiology of SS and MF appears to be different. Campbell et al. [14] suggest that this difference stems from the cell of origin, postulated to be central memory T-cells in SS, and skin-resident effector memory T-cells in MF. This biological difference is supported by differences in gene expression, mutational landscape, PD1 expression, and other molecular profiles [15–19].

Systemic treatment selection is guided by prognostic features, incorporating stage, and immunophenotypic and molecular findings, and patient-specific factors such as age and comorbidities [20, 21]. Poor prognostic features include advanced stage, presence of tumors, age > 57 years, male gender [9, 22, 23], increased lactate dehydrogenase [22], large-cell transformation [10, 11, 24, 25], presence of an identical T-cell clone in blood and skin [26], high Sézary cell count [27], blood eosinophilia [28], folliculotropic MF variant [29, 30], and poor response to first-line treatment [31, 32•]. The identification of prognostic markers has been facilitated by the Cutaneous Lymphoma International Consortium; indeed, their international collaborative database project identified specific prognostic markers in a *retrospective* review [32•], and led to the PROCLIPI (*prospective* Cutaneous Lymphoma International Prognostic Index) study.

The rarity of CTCL makes the development of robust evidence-based treatment guidelines difficult. Randomized controlled studies are uncommon, and the literature is composed predominantly of retrospective, cohort, and early-phase studies. International consensus guidelines are available; however, the lack of comparative trials means that there is no clear algorithmic approach to treatment [7, 8, 27, 33–36]. Heterogeneity in treatment approaches has thus been found across specialist centers worldwide, and in particular, between US and non-US centers. A recent retrospective study involving 21 international centers (the UK, Italy, the Netherlands, Greece, Spain, France, Germany, Israel, USA, Australia,

Table 3 Quaglino et al. [37••] report on most common treatment approaches by stage

Stage	First-line treatment	Second-line treatment
IIB	Bexarotene	1. Local radiotherapy
		2. Phototherapy
		3. Total skin electron beam therapy
		4. Gemcitabine
IIIA	Methotrexate	
IIIB	Photopheresis alone or in combination	
IVA1	Photopheresis	1. Interferon alfa
		2. Chlorambucil
IVA2	Poly-chemotherapy	Not reported
IVB	Poly-chemotherapy	Not reported

Japan, and Brazil) involving 853 patients with advanced-stage CTCL, reported the most common treatment approaches by stage. These are shown in Table 3 [37••]. The authors describe up to 24 different single or combination therapies as first-line treatment, with no one treatment taking more than 15% of the "market share." Their data demonstrates a preferential use of skin-directed therapies in stages IIB, III, and IVA1, while polychemotherapy is most frequently used in stages IVA2 and IVB. However, given the key finding of the adverse survival outcome of patients receiving chemotherapy first-line, the authors support preferential use of immune-modifiers (interferon-alfa and/or extracorporeal photopheresis) as first-line therapy, followed by chemotherapy, targeted therapies, or allogeneic transplant, for patients with stage IVA2 and IVB disease.

We present here current and potential treatment options for patients with advanced-stage MF and SS. In particular, we review the different treatments identified by Quaglino et al. [37••] to aid the clinician in selecting between therapies for their patients.

Methods

The Ovid Medline electronic database was searched for studies published in English. Search terms included cutaneous T-cell lymphoma OR mycosis fungoides OR Sézary syndrome AND systemic treatment including MeSH terms. These electronic searches were supplemented by review of bibliographies and key references cited.

Discussion

In general terms, single-agent systemic therapy is often used when skin-directed therapy fails or in cases of advanced-stage disease. Correct staging of patients with MF and SS is imperative when selecting between systemic treatment options, as this is recognized as the major predictor of outcome [33, 35]. In addition to disease stage, clinicians must also consider individual patient disease characteristics, comorbidities, treatment availability and access, and potential toxicities.

Bexarotene

In use since 1999, bexarotene is a synthetic retinoid of the "rexinoids" subclass, so named due to their selective activation of retinoid X receptors which regulate a range of cellular functions including differentiation, proliferation, and apoptosis [38]. Specifically in CTCL, bexarotene activates the p53/p73-dependent cell cycle inhibitory pathway [38]. Response rates in advanced-stage disease were originally described in moderately large phase II and III studies [39, 40]. However, these early studies used comparatively simple response criteria, such as physician global assessments, compared to those in current use (i.e., mSWAT [27, 41]).

Bexarotene was one of the control arms of the recently reported international, open-label, randomized, phase 3 multicenter ALCANZA study [42••], comparing brentuximab vedotin (BV) with physician's choice of either bexarotene or methotrexate. This study included 128 patients with CD30+ CTCL who had received at least one (maximum of 4) prior systemic therapy; both groups were well matched for number of prior systemic therapies; however, the types of therapies used were not enumerated in detail. Using updated response criteria [27], the overall response rate (ORR) of the physician's choice group was a modest 12.5%. Progression-free survival (PFS) was only 3.5 months in the physician's choice group. However, among the responders in the physician's choice group, the median duration of response (DoR) was 18.3 versus 15.1 months in the BV group, suggesting that a minority of patients can achieve meaningful and durable responses to bexarotene or methotrexate.

Bexarotene may be more active if given earlier in the disease course; moreover, if patients respond, treatment can continue indefinitely [43, 44]. It has been shown to be better tolerated if given with concurrent lipid-lowering medications

[45]. Combination with other treatments such as extracorporeal photopheresis (ECP) [45, 46], interferon-alfa [45, 47], methotrexate [48], denileukin diftitox [49, 50], gemcitabine [51], pralatrexate [52], and psoralen with ultraviolet-A (PUVA) [45, 53, 54] has been reported.

The most common adverse events (AEs) associated with bexarotene are hypertriglyceridemia (82%), fatigue (32%), hypercholesterolemia (30%), hypothyroidism (29%), and headache (20%) [42••, 53].

Interferons-Alfa and Gamma

Interferons are naturally occurring immunomodulatory proteins with cytostatic and antiviral properties. Interferon-alfa (IFN-α) is primarily produced by leukocytes, and in CTCL, works through the inhibition of IL-4 and IL-5 production by malignant T-cells, as well as by activating CD8+ T-cells and NK cells. This augments the Th1 cell-mediated response and suppresses the Th2 cytokine production of malignant T-cells [55, 56], resulting in a net correction of the Th1/Th2 response imbalance seen in CTCL [57]. More recently, Furudate et al. [58] have suggested that IFN-α may also mediate its effects through the modulation of tumor-associated M2 macrophages.

The use of IFN-α in CTCL was first reported in 1984 [59]. A long-term follow-up study of IFN-α has shown an initial complete response (CR) rate of 41%; however, relapse was observed within 57% of patients at a mean period of 7.5 months, regardless of clinical stage [60]. The efficacy of IFN-α was further supported in a more recent study by Hughes et al. [61], which demonstrated that, when given as first-line or last-line therapy, there was no difference in time to next treatment (TTNT) between IFN-α and chemotherapy, but that IFN-α performed significantly better than chemotherapy when given as midline (2nd-4th line) treatment.

The most important AEs of IFN-α include hypothyroidism, weight loss, anorexia, and mood changes. IFN-α can be used in combination with other agents such as bexarotene [45, 47] and ECP [62, 63]. It has also been shown to be moderately effective in combination with PUVA [64], narrow-band UVB phototherapy (NBUVB) [65], and IFN-gamma [66]. Combination with retinoids does not appear to increase response rates [47, 67]. It is potentially very useful in patients with eosinophilia, given its inhibitory effects on eosinophil chemotaxis and activation [68].

Interferon gamma (IFN-γ) has also been used in CTCL. Early phase I [69] and phase II [70] studies reported partial responses (PR) in 31% of patients and no CR, with AEs including fever, fatigue, myalgia, headache, and reversible liver and triglyceride derangements. More recently, Sugaya et al. [71] reported an ORR of 60% in their multisite, phase II study of intravenous IFN-γ in 15 patients with stage IA-IIIA MF.

Extracorporeal Photo-chemotherapy/Photopheresis (ECP)

First introduced as a potential therapy for erythrodermic MF/SS in 1987 [72], ECP involves the extracorporeal exposure of leucocyte-rich plasma to 8-methoxypsoralen and UVA radiation, before re-infusion into the patient. The National Comprehensive Cancer Network, the British Photodermatology Group, and the EORTC European Consensus Guidelines all recommend ECP as first-line treatment for erythrodermic MF and SS [73].

As monotherapy, response rates to ECP are around 63% (43–100%), with CR rates of 20%. TTNT is between 9.2 and 12 months [61, 73, 74]. Treatment schedules vary between centers, and maintenance treatments may be given according to disease response and severity [73, 75]. The addition of other immune-modulating therapies such as bexarotene [46], IFN-α [76–78], localized radiotherapy and electron beam therapy [79], chemotherapy [79], or the combination of bexarotene and IFN-alfa may increase response rates in some patients [27].

Methotrexate

Methotrexate is a synthetic folic acid analogue which acts through competitive inhibition of dihydrofolate reductase, inhibiting purine and pyrimidine synthesis [80]. It has demonstrable benefit in CTCL even at low doses, with an ORR of 33% in T2 disease and 58% in T4 disease [81]. However, these early studies used comparatively simple measures of response compared to current criteria [27], and, moreover, measured response only in the skin compartment. Like bexarotene, methotrexate was one of the control arms of the ALCANZA study [42••], with modest ORR and PFS rates, as outlined earlier. A minority of patients can, however, achieve durable responses.

A detailed description of reported AEs is available in the article by Shen et al. [80]. These authors describe the most common AEs as nausea, anorexia, fatigue, and malaise. Opportunistic infections, pulmonary toxicity, and mucositis can also occur but are less common.

Brentuximab Vedotin

Brentuximab vedotin (BV) is a chimeric monoclonal antibody-drug conjugate, consisting of an anti-CD30 antibody linked to a potent microtubule-disrupting agent, monomethyl auristatin E (MMAE) [82]. Endocytosis of this conjugate results in cell cycle arrest and apoptosis. CD30 is relatively restricted in its expression to a small subset of activated leukocytes, as well as a number of hematologic malignancies including CTCL, making it a rational therapeutic target. Traditionally, the standard definition of CD30 positivity was ≥ 75% of tumor cells expressing CD30 [83]. However, the

following studies have redefined this cutoff, showing that even patients with lower percentages of CD30 expression as assessed by immunohistochemical methods can achieve meaningful disease responses.

Two phase II studies of BV in MF and SS have been published, using the same dosing schedule of 1.8 mg/kg administered once every 3 weeks to a total of 16 cycles. Kim et al. [84] reported on 30 patients with MF or SS with variable CD30 expression (positive defined as 10% or higher by immunohistochemistry). An objective global response was seen in 21 patients (70%), with one patient achieving CR. The majority of the population was advanced stage, with no statistically significant difference in response rates between early or advanced stages. However, patients with a CD30 expression of < 5% had a much lower likelihood of response compared to higher CD30 levels. The phase II trial reported by Duvic et al. [85] included 48 patients with MF or SS. When stratified according to CD30 expression, ORR was similar between all subgroups (ORR 50–58%). Median time to response was 12 weeks (3–39) with median DoR of 32 weeks (3–94).

More recently, the phase III ALCANZA study [42••] compared BV to physician's choice, as previously outlined. Results demonstrated a clear benefit of BV, as reflected in an ORR at 4 months (ORR4) of 56.3 versus 12.5%, the proportion of patients achieving a CR to either agent (16 versus 2%), and a median PFS of 16.7 versus 3.5 months. Treatment with BV demonstrated a 3.7-fold improvement in the risk of progression, and a median PFS benefit of 13.2 months. While the median DoR was less for BV compared to physician's choice (15.1 versus 18.3 months), median DoR in those with skin response showed a benefit from BV (20.6 versus 18.3 months); these differences were not statistically significant, however. This study is a first in CTCL, comparing a novel systemic treatment with standard therapies in a randomized phase III trial.

Common AEs of BV include peripheral neuropathy, gastrointestinal upset (nausea, diarrhea, vomiting), alopecia, pruritus, pyrexia, decreased appetite, and fatigue [42••].

Monoclonal Antibodies

Mogamulizumab is a humanized monoclonal antibody (mAb) targeting CCR4, a chemokine receptor expressed on T-cells in approximately 40% of patients with CTCL [13]. Approved for use in CTCL in Japan, and recently the USA, mogamulizumab has a reported ORR of 35% with a CR rate of 14% ($n = 37$) [86]. Of note, mogamulizumab appears particularly effective in patients with erythroderma and peripheral blood involvement. The phase III MAVORIC trial compared mogamulizumab to vorinostat in 372 patients, and demonstrated a statistically significant benefit in ORR of 21% in MF and 37% in SS ($p < 0.0001$), with a median PFS of 6.7 months [87••]. AEs include flu-like symptoms, headache, rash, and infusion reactions [88], as well as two reported cases of Stevens-Johnson syndrome [89, 90].

Alemtuzumab is a humanized mAb targeting CD52, which is expressed in high levels on malignant T-cells [91]. It is particularly effective in patients with SS, which may reflect its effect on circulating rather than skin-resident malignant T-cells [13, 92]. Variable dosing regimens have been reported in the literature, including higher-dose, intravenous regimens [91–94], and lower doses given intravenously or subcutaneously [95–98]. Early studies reported ORR of 38–86% with a CR rate of 47% [91, 93]. A later study reported ORRs of 70% in SS patients and 25% in MF. Median time to progression was 3.4 months; however, five patients remained progression free for over 2 years [92]. Most common AEs include infusion-related side effects, and opportunistic infections including CMV reactivation [13, 93, 99]. While alemtuzumab can achieve rapid and effective symptomatic control and leukemic debulking, the attendant risks of profound immunosuppression make it suitable for only a small number of patients.

Histone Deacetylase Inhibitors

Histone deacetylases (HDACs) are key effector proteins controlling gene transcription including those involved in apoptosis and tumor cell growth. Their effect is mediated through the removal of acetyl groups from core histone proteins that control access to transcription factors [13, 100]. HDAC inhibitors (HDACi) cause inhibition of cell proliferation and differentiation, and are thought to modulate gene expression to induce cellular apoptosis. Other possible mechanisms include alteration of angiogenic signaling, alteration of microtubule function, induction of MHC antigen presentation, and suppression of IL-2-mediated gene expression [101, 102]. Those currently in use for CTCL are vorinostat and romidepsin. There is no comparative data to suggest the superiority of either. HDACi are reported to have a median TTNT of 4.5 months and DoR up to 12 months [61].

1. Vorinostat has been FDA approved for CTCL since 2006, and is administered orally. Duvic et al. [102] reported results of the phase IIa clinical trials, showing a meaningful PR (defined as > 50% reduction in disease burden) in 24% of patients ($n = 33$), noting that this was a cohort of heavily pretreated patients with refractory CTCL. Olsen et al. [41] reported the phase IIB trial results ($n = 74$) and found that an ORR of 29.7% with a median time to response for patients with stage IIB or higher was 56 days. Unfortunately the DoR was not reached. The phase III MAVORIC trial ($n = 372$, with 186 patients treated with vorinostat) [87••] reported an ORR of 7.1% in MF and 4.1% in SS with a median PFS of 3.1 months in the vorinostat-treated cohort. The discrepant ORRs between earlier studies and the later phase III may reflect differing

sample sizes, differing number of prior systemic therapies (two versus three), or different assessment tools (response assessed in skin only in phase II studies, versus in all compartments in the phase III study). Most common AEs include fatigue (52.3%) and gastrointestinal symptoms (diarrhea (52.3%), nausea (40.7%), dysgeusia (27.9%), and anorexia (24.4%) [102]). Thrombocytopenia is common and can be dose limiting [102].

2. Romidepsin has been FDA approved since 2009 for CTCL patients who have received at least one prior systemic therapy, and is administered intravenously. Piekarz et al. [103] reported results from a phase II multi-institutional trial in patients with CTCL who had received no more than two prior systemic therapies. Seventy-one patients were included, of whom 87% had advanced-stage disease. ORR was 34%, with PR seen in 20 patients and CR in 4 patients. Whittaker et al. [104] conducted an international phase II study in 96 patients with stage IB-IVA CTCL, with advanced-stage disease in 71% of patients. The ORR was 34%, with six CRs. The median time to response was 2 months, with a median DoR of 15 months. Updated outcome data reported durable responses in a number of patients, and confirmed that re-treatment was feasible [105]. AEs are similar to vorinostat, with nausea and fatigue being most commonly reported. While there is a clear role for romidepsin in CTCL treatment, data around predictors of response is lacking, and comparative trials would be helpful [106].

Denileukin Diftitox

Denileukin diftitox (DD) is a recombinant IL-2-diphtheria toxin fusion protein that targets IL-2 receptors on T-cells. Endocytosis of DD inhibits protein synthesis leading to cell death [49]. It has proven efficacy in patients with both early and advanced-stage CTCL [107], and has been used as monotherapy and in combination with bexarotene with moderate success [49]. A phase III study comparing two doses of DD and placebo reported an ORR of 44%, with a CR rate of 10% and a PR rate of 34% in the pooled DD cohorts compared to 15.9% in the placebo-treated group [108]. ORR was higher in the DD group treated with a higher dose. PFS was significantly longer in the DD groups (median > 2 years) compared to placebo (median 124 days). Similar response rates can be achieved with re-treatment [109].

AEs include nausea, pyrexia, fatigue, rash, liver function abnormalities, hypothyroidism, vision changes, and capillary leak syndrome [107, 108]. Production of this agent was discontinued in 2014, and phase II trials of a newer, revised formulation (E7777) are ongoing [107].

Systemic Chemotherapy

Many chemotherapy agents have proven activity in CTCL. However, none has proven superior, and a key retrospective study has highlighted the inability of chemotherapy to provide durable disease control [61]. Some clinicians use multiagent regimens, while others use single-agent regimens with the aim of reducing toxicity. Due to its frequent AEs and limited effect on survival, chemotherapy is usually reserved for advanced-stage disease with bulky nodes, disseminated tumors, or visceral involvement [37••, 99]. We recommend that chemotherapy should be used only if previous treatments are contraindicated or have failed [12, 61].

1. Doxorubicin is an anthracycline with proven efficacy for nodal lymphomas and solid tumors. The pegylated liposomal form has reduced toxicity, possible improved efficacy, and a longer half-life. It is currently the most commonly used anthracycline for advanced-stage CTCL [13], with an ORR of 41–88%, and a time to relapse of 13 months [110, 111].
2. Gemcitabine is a nucleoside analogue of deoxycytidine that inhibits DNA synthesis. Gemcitabine is one of the most effective single-agent chemotherapy agents for CTCL, with an ORR of 48–68% and a CR rate of 9–20% [111].
3. Pentostatin is an inhibitor of adenosine deaminase with selective toxicity to lymphocytes. Pentostatin has been shown to have an ORR rate of 14–71%, with a CR rate of up to 25%, and may have an even higher response rate in patients with SS (up to 71%) [111].
4. Bendamustine is an intravenous nitrogen mustard-alkylating agent approved for use in the treatment of indolent B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia. There are two studies evaluating its use in CTCL. The first reported an ORR of 50% but did not analyze outcomes specifically in the MF subgroup [112]. The second reported only PR in three patients with advanced-stage MF/SS [113].
5. Chlorambucil is an alkylating agent that cross links DNA during all phases of the cell cycle. It has been used in CTCL as monotherapy and in combination with glucocorticoids [114]. As per Quaglino et al. [37••], it is commonly used outside the USA as first-line therapy for advanced stages, but large-scale clinical trial data as to its efficacy is lacking.
6. Combination therapy has been reported in several older studies: Fludarabine and cyclophosphamide showed a ORR of 58% in stage IIB-III disease with a time to relapse of 10 months [115]. Etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone in patients with stage IIB-IV disease had an ORR of 80% with a time to relapse of 8 months [116]. Cyclophosphamide, doxorubicin,

vincristine, and prednisone (CHOP) chemotherapy has been used in stage IIB disease with an ORR of 66% [117].

Agents Under Investigation

As the possible pathogeneic mechanisms in CTCL are uncovered, more therapeutic agents may become available. We list here some treatments which may merit closer examination in the clinic:

Pralatrexate is a novel antifolate with high affinity for the reduced folate carrier (RFC), which is highly expressed in malignancy [118]. While its mode of action is similar to methotrexate, pralatrexate has been shown in vitro and in vivo to be 5 to 40 times more cytotoxic than methotrexate [119].The PROPEL study (Pralatrexate in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma) included 12 patients with transformed MF. In this subset, ORR was 25% by independent central review (58% by investigator assessment) [120], with a median DoR of 2.2 months [121]. Building on this, preclinical studies involving the combination of pralatrexate with other agents such as gemcitabine and HDACi are underway [118]. The most common AEs reported are mucositis (22–58%), fatigue (43%), nausea (39%), and thrombocytopenia (32%) [120, 122].

Lenalidomide is an oral analogue of thalidomide. It is immunomodulatory through its effects on T-cell and natural killer (NK) cell activation, but is also pro-apoptotic, antiangiogenic, and antiproliferative. A multicenter phase II trial of lenalidomide as monotherapy in 32 patients with refractory MF and SS reported PR was achieved in 28%. Median PFS was 8 months, and median DoR was 10 months [123].

Humanized Monoclonal Antibodies

- Anti-CD158K (IPH4102) is targeted against KIR3DL2, a NK cell immunoglobulin-like receptor expressed on NK and CD8+ cells. Activation of this receptor regulates the effector functions of the innate immune system. There is a reported strong correlation between the level of CD158K+ cells and circulating Sézary cells, and as such, CD158K may be used as a surrogate for tumor burden in SS [124]. Phase I and II trials are underway.
- Ipilimumab is directed against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). CTLA-4 is expressed by activated T-cells and acts to downregulate the immune response by inhibiting T-cells via CD80 and CD86. Ipilimumab blocks this inhibitory signal and promotes cytotoxic destruction of malignant T-cells. Ipilimumab has shown potential as a treatment for MF in a case study [125] and is currently undergoing a phase II trial.
- Nivolumab and pembrolizumab (so-called checkpoint inhibitors) target the programmed cell-death-1 (PD-1) receptor. PD-1 is expressed on follicular helper T-cells, and functions to promote self-tolerance by promoting apoptosis of antigen-specific T-cells while enhancing T-cell regulatory function [126]. PD-1 expression is high in patch and plaque-stage MF, and despite an ORR of only 15% in early studies, these mAbs may be useful in early-stage disease. Additionally, PD-1 is expressed in higher levels in CD4+ T-cells in SS (89%) compared to MF (13%) [15, 20], suggesting that PD-1-targeted therapies may be more effective in SS. A phase II trial of pembrolizumab in patients with stage IB-IVB MF/SS is currently underway.

Histone Deacetylase Inhibitors

- Panobinostat: Duvic et al. [127] reported on a phase II trial of panobinostat in 103 patients with refractory CTCL. ORR was 17.3% in all patients, with a slightly higher ORR (20%) in those patients who were bexarotene-naive. The median PFS was between 3.7–4.2 months, and median DoR was 5.6 months.
- Belinostat is approved by the FDA for PTCL with no specific trials in CTCL reported to date [13].
- Quisinostat is a hydroxamate, second-generation, orally available pan-histone deacetylase inhibitor. A recent multicenter phase II trial demonstrated a response rate of 24% with DoR from 2.8 to 6.9 months [128].

A-dmDT390-bisFv(UCHT1) (trade name Resimmune) is a second-generation recombinant immunotoxin comprising two anti-CD3-epsilon antibody fragments fused to diphtheria toxin. ORR was 36% in a phase II trial in CTCL [129].

Bortezomib is a first-generation 20S proteasome inhibitor with preclinical data that suggest it is likely to be effective in CTCL [130, 131]. A phase II trial in relapsed/refractory CTCL reported an ORR of 67% and a CR rate of 17% [132].

Duvelisib is an inhibitor of the intracellular signal transducer enzymes phosphoinositide-3 kinase (PI3K) delta and gamma, which are involved in immune cell proliferation, survival, and cellular trafficking. Dysregulation of PI3K has been demonstrated in MF and SS [133]. A phase I trial investigating the efficacy of duvelisib in CTCL showed an ORR of 38% [134]. Another PI3K inhibitor, BKM120 (buparlisib), has also shown promising preclinical activity, and has been shown to potentiate HDACi activity in MF/SS [135].

Everolimus is an mTORC1 inhibitor which inhibits the mammalian target of rapamycin (mTOR), a member of the PI3K

family. Aberrant signaling through the PI3K/Akt/mTOR pathway has been implicated in CTCL, particularly in advanced stages [136]. Treatment of seven MF patients with everolimus produced a 75% response rate [137]; however, further larger studies are required. Additionally, drug combinations, such as the rapamycin-MNK inhibitor pairing which appeared synergistic in vitro in a CTCL cell line [138], is another potential therapeutic avenue.

Tofacitinib is a Janus kinase 3 (JAK3) inhibitor, targeting JAK3, a tyrosine-protein kinase expressed predominantly in hematopoietic cell lines and involved in cell transcription. JAK3 mutations have been identified through genetic sequencing of MF tumors [20], and therefore, inhibitors have a putative therapeutic role in CTCL.

Hypomethylating Agents

Azacitidine is a cytotoxic analogue of the nucleoside cytidine. Its effects are mediated through DNA hypomethylation [139], in part through the enhanced transcription of tumor suppressor genes. Azacitidine has additionally been reported to be efficacious in peripheral T-cell lymphoma (PTCL) [140–142]. CTCL genomic sequencing has demonstrated commonly occurring mutations in genes associated with DNA methylation and epigenetic modification, as well as hypermethylation of tumor suppressor gene promoter regions [16–18, 143–146]. Treatment of a Sézary cell line with decitabine (5-aza-2′-deoxycytidine) resulted in cellular apoptosis [147]. The use of single agent azacitidine has not been reported in CTCL patients; however, based on results in PTCL and extrapolating from our understanding of the CTCL genetic landscape, it would be a rational choice for exploration in the clinic.

Conclusion

The systemic treatment of advanced-stage cutaneous T-cell lymphomas (MF and SS) is challenging. We have focused here on the many treatment options currently available as well as those that are potentially on the horizon. Although a rare disease, the morbidity and high mortality associated with CTCL deserves the attention of the scientific and medical community to identify more effective therapies for this disease.

Compliance with Ethical Standards

Conflict of Interest Louise Photiou declares that she has no conflict of interest.

Carrie van der Weyden declares that she has no conflict of interest.

Christopher McCormack has received compensation from Takeda Pharmaceuticals and MSD for participation on advisory boards.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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