Best Practice & Research Clinical Haematology 32 (2019) 239–252

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/issn/15216926

Leukaemic variants of cutaneous T-cell lymphoma: Erythrodermic mycosis fungoides and Sézary syndrome

Xochiquetzal U. Martinez[a], Cosimo Di Raimondo[a,c], Farah R. Abdulla[a], Jasmine Zain[a], Steven T. Rosen[a,b], Christiane Querfeld[a,b,*]

[a] City of Hope National Medical Center, 1500 E. Duarte Road, Duarte, CA 91010, USA
[b] Beckman Research Institute, 1500 E. Duarte Road, Duarte, CA, 91010, United States
[c] Policlinico Tor Vergata, Viale Oxford 81, 00133, Rome, Italy

ARTICLE INFO

Keywords:
Mycosis fungoides
Sézary syndrome
Cutaneous T-cell lymphoma
Erythrodermic
Leukaemic variants
Treatment regimen
Therapeutic strategies
Investigational therapies
Supportive care

ABSTRACT

Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common types of cutaneous lymphoma, accounting for approximately 60% of cutaneous T-cell lymphomas. Diagnosis requires correlation of clinical, histologic, and molecular features. A multitude of factors have been linked to the aetiopathogenesis, however, none have been definitively proven. Erythrodermic MF (E-MF) and SS share overlapping clinical features, such as erythroderma, but are differentiated on the degree of malignant blood involvement. While related, they are considered to be two distinct entities originating from different memory T cell subsets. Differential expression of PD-1 and KIR3DL2 may represent a tool for distinguishing MF and SS, as well as a means of monitoring treatment response. Treatment of E-MF/SS is guided by disease burden, patients' ages and comorbidities, and effect on quality of life. Current treatment options include biologic, targeted, immunologic, and investigational therapies that can provide long term response with minimal side effects. Currently, allogeneic stem cell transplantation is the only potential curative treatment.

Introduction

Primary cutaneous lymphomas (PLC) represent a spectrum of extranodal non-Hodgkin lymphomas (NHL) with unique clinical, histopathological, phenotypic, molecular, and prognostic features that differ from histologically similar systemic lymphomas, and require different therapeutic approaches. Thus, the World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC) created a separate consensus classification system for PCL, which was recently updated in 2018, that serves as the gold standard for diagnosis and categorization of PCL. Cutaneous T-cell lymphomas (CTCL) comprise a heterogeneous group of primary extranodal NHLs that arise from the malignant transformation of mature postthymic T cells. In contrast to systemic lymphomas, the majority of PCLs are of T-cell origin, with CTCLs accounting for 75–80% of PCLs.

Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common forms of CTCL, characterized by skin homing $CD4^+$ T cells. Clinically, MF presents as cutaneous patches, plaques, tumours, and/or erythroderma, with or without extracutaneous involvement; though patients with erythrodermic MF (E-MF) often present with a low burden of circulating malignant T cells (Sézary cells). SS, in contrast, is the leukaemic variant of CTCL that manifests with erythroderma, peripheral lymphadenopathy, and a high

* Corresponding author.
E-mail addresses: xomartinez@coh.org (X.U. Martinez), cdraimondo@coh.org, cosimodiraimondo@gmail.com (C. Di Raimondo), fabdulla@coh.org (F.R. Abdulla), jazain@coh.org (J. Zain), srosen@coh.org (S.T. Rosen), cquerfeld@coh.org (C. Querfeld).

https://doi.org/10.1016/j.beha.2019.06.004
Received 31 May 2019; Accepted 5 June 2019

burden of circulating Sézary cells [1]. Although early-stage MF patients have an indolent course, those with advanced-stage MF/SS have compromised survival [1,2]. MF and SS share overlapping features, but are considered distinct entities. This review will focus on erythrodermic CTCL (E-CTCL), which includes E-MF and SS.

Epidemiology

CTCLs make up approximately 3.9% of all NHLs and have an estimated age-adjusted incidence rate (IR) of 6.4–7.7/1,000,000 person-years in the United States (US) [3,4]. While the incidence of CTCL had been on the rise since the early 1970s [4], likely, in part, due to improvements in diagnostic methods, it has recently been determined to be stable since 1998 [5]. In contrast to the incidence, the prevalence of CTCL is relatively high given the excellent survival for most subtypes, with gross estimates ranging from 25,000 to 50,000 patients living with CTCL in the US [6].

MF and SS are the classic types of CTCL. MF is the most prevalent, accounting for approximately 60% of CTCLs. SS, however, is rare, and comprises roughly 2.5–3% of cases, with an estimated incidence of 0.3 per million persons [4,7]. MF typically affects older individuals, with a median age at diagnosis of 55–60 years and peak of around 80 years, and has a male-to-female incidence rate ratio that ranges from 1.6 to 1.9:1; though no gender preference was noted in patients less than 30 years of age [3–5]. MF occurs at higher rates in Blacks than in any other ethnic group [1,3]. SS has also been noted to occur at higher rates in men and older individuals. However, unlike MF, the incidence of SS was noted to be higher in Whites than Blacks. Though, due to the rarity of SS, minimal epidemiologic data exists [4].

Clinicopathologic features

MF, in the early stages, characteristically presents with well-defined, scaly, erythematous patches and/or plaques that are often pruritic. Progression of MF is defined by the development of tumours and/or erythroderma. Erythroderma, however, can develop with or without a background of pre-existing cutaneous lesions, and is a hallmark of both E-MF and SS. E-MF and SS represent a spectrum of E-CTCL; and while SS may be preceded by E-MF, it usually develops de novo [8]. Other features that are common in E-CTCL are alopecia, palmoplantar keratoderma, and ectropion (Fig. 1).

Typical histologic findings in MF are an epidermotropic infiltrate consisting of medium-sized, atypical lymphocytes with hyperconvoluted (cerebriform) nuclei, admixed with small lymphocytes and histiocytes. In early stage disease, skin biopsies demonstrate a superficial perivascular or band-like infiltrate in the dermis with varying degrees of epidermotropism of single cells or clusters (Pautrier microabscess) of atypical lymphocytes [7,9]. Tumour lesions, conversely, show a diffuse, dense, and deep dermal infiltrate, with either diminished or absent epidermotropism of atypical lymphocytes [10]. The histological findings in E-CTCL are similar to those in MF, but tend to be more subtle. The neoplastic infiltrate is often sparse, with minimal, if any, epidermotropism. In up to one-third of biopsies, the findings are non-specific [7]. Thus, immunohistochemistry and blood flow cytometry are essential for the accurate diagnosis of E-CTCL.

The malignant cells are a monoclonal expansion of predominantly TCR αβ, CD45RO + memory T cells. They typically have a $CD3^+$, $CD4^+$, CD8- immunophenotype, with frequent loss of CD5, CD7, and CD26, and increased CD4:CD8 ratio. While CD7 is normally expressed on approximately 90% of $CD4^+$ T cells, it is found to be either completely or partially lost on circulating neoplastic cells in 60–70% of SS cases. However, altered expression of CD7 has been noted in benign inflammatory dermatoses, and thus, loss of CD26 is more specific for identifying Sézary cells [8,11].

No definitive marker exists to delineate E-CTCL, though there are notable changes in the chemokine receptor profile of malignant T cells. Based on the differential expression of chemokine receptors, MF and SS, while related and sharing overlapping features, are considered two distinct entities that derive from separate memory T cell subsets. The leukaemic CTCL cells in SS are central memory T cells (T_{CM}), which recirculate in the blood and lymph nodes. They show co-expression of CCR4, CCR7, and L-selectin, with variable

Fig. 1. Right lower lid ectropion (a); patchy (b) and diffuse (c) erythroderma with alopecia; diffuse, exfoliative erythroderma with hyperkeratotic plaques on elbows (d); plantar keratoderma (e); and chronic thickening of the skin of the dorsal hands, impetiginized, with fissuring and onychodystrophy (f) in patients with E-CTCL.

expression of CLA. About 20% of T_{CM} are also found in skin, giving rise to new populations of tissue-tropic effector cells when rechallenged with antigen. MF, on the other hand, has been shown to be a malignancy of CCR4+, CCR7- skin resident effector memory T cells (T_{EM}), which do not recirculate. Clonal malignant T cells from MF skin lesions demonstrated expression of CLA and CCR4, but lacked co-expression of CCR7 and L-selectin, and thus had a phenotype characteristic of T_{EM} [12].

PD-1 and KIR3DL2 (CD158k) have also been noted to have differential expression in MF and SS, reinforcing the view that MF and SS are distinct entities. PD-1 and KIR3DL2 have shown increased levels in SS, compared to MF [13,14], and have emerged as important therapeutic targets. Analysis of TCR gene rearrangement in the skin and blood for clonality can also aid in the diagnosis of E-CTCL. However, while presence of TCR clonality alone is not definitive for malignancy, as it can be present in benign dermatoses, when taken in conjunction with the entire clinicopathologic picture, it can provide supporting evidence for diagnosis [15].

Patients with E-CTCL have either stage III or IV disease, with exact stage determined by degree of nodal, visceral, and blood involvement. To distinguish E-MF from SS, the International Society for Cutaneous Lymphoma (ISCL) recommended classification based on the degree of blood involvement, which was categorized as follows: no blood tumour burden (B0), defined as $\leq$5% Sézary cells on peripheral smear, low blood tumour burden (B1), defined as > 5% but $\leq$20% Sézary cells, or high blood tumour burden (B2), defined as > 1000 cells/μL or > 20% Sézary cells [8,11]. While patients with B0 or B1 blood involvement are classified as E-MF, B2 blood involvement, plus clonal rearrangement of the TCR in the blood that is relevant to the clone in the skin, is necessary for the diagnosis of SS. The ISCL-EORTC further expanded the criteria for B2 classification to include a CD4:CD8 ratio $\geq$10, or expanded $CD4^+$ T cells with abnormal immunophenotype, specifically $\geq$40% loss of CD7- or $\geq$30% loss of CD26 [16].

Aetiology and pathogenesis

The aetiopathogenesis of CTCL remains largely unknown. Due to the rarity of CTCL, data are sparse and primarily derive from studies on MF, given that it is the most common type of CTCL. While numerous hypotheses have been posited, many studies show conflicting data or lack validation. Though the heterogeneity in clinical presentation and behaviour of CTCL raises the likelihood that the development of CTCL is attributable to more than one aetiology.

CTCL derives from skin-homing, memory T-cells that clonally expand within a background of chronic inflammation. It is believed that chronic antigenic stimulation, combined with underlying cytogenetic abnormalities, results in the unchecked clonal proliferation of these atypical lymphocytes [10,17]. A wide variety of environmental and occupational exposures, and iatrogenic factors have been implicated as causative agents; however, no definitive evidence of any hypothesized association exists [18–20]. A few studies have raised the possibility of a self-stimulatory pathway contributing to the pathogenesis of CTCL, as they demonstrated the co-localization of antigen presenting cell (APC) receptors, B7 and CD40, and their respective T-cell ligands, CD28 and CD40L, on neoplastic lymphocytes within MF lesions; though this was also demonstrated in chronic, benign conditions, such as psoriasis [21,22].

Bacterial and viral pathogens have been suggested to play a role. *Staphylococcus aureus*, in particular, has been the focus of numerous studies given that cutaneous colonization is often seen in erythrodermic MF, and SS patients. Keratinocytes of MF patients have shown increased expression of toll-like receptors (TLR) 2, 4, and 9 [23]. TLR2, specifically, recognizes pathogen-associated molecular patterns (PAMPs) from *S. aureus* [24]. Thus, the increased expression of TLRs may be related to the cutaneous colonization with *S. aureus*. Additionally, while cutaneous colonization with *S. aureus* has been associated with disease progression, clinical improvement after eradication of *S. aureus* with a course of antibiotics has been noted [25]. Staphylococcal exfoliating toxin and toxic shock syndrome toxin-1 stimulate a proliferative response in Sézary cells. This clonal expansion is further enhanced by the addition of interleukin-1 (IL-1). Notably, the toxins induce IL-1 production in keratinocytes [26].

Investigations of viral pathogens have focused on EBV, CMV, and HTLV-I. While MF patients are often found to be seropositive for EBV and CMV, the significance of this finding, if any, has yet to be elucidated [27]. Conversely, while most CTCL patients, aside from those with ATLL, demonstrate no serologic evidence of HTLV-I, one study reported the presence of HTLV-I proviral DNA sequences in extracts of peripheral blood mononuclear cells; thus, positing an association of HTLV-I with the development of MF [28,29]. However, the results of this study remain controversial.

Immunosuppression and/or immunosuppressive therapy may be risk factors for the development of CTCL. Cases have been documented in patients following organ transplantation [30,31], after treatment for Hodgkin's disease [32], in HIV-positive patients [33,34], and subsequent to use of biologic therapy, specifically anti-TNFα, for the treatment of immune-mediated disorders [35,36]. Lastly, while no definitive genetic inheritance or predisposition has been established, two studies have shown an association of MHC class II alleles HLA-DRB1*11 and DQB1*03 with MF [37,38].

More recent studies have demonstrated increasing evidence that apoptotic resistance, as opposed to uncontrolled cellular proliferation, may have a more significant role in the pathological process responsible for the development of CTCL. This acquired resistance is mediated via the extrinsic apoptotic pathway and influenced by the tumour microenvironment. Among other mechanisms of apoptotic dysregulation, malignant T cells display resistance to activation induced cell death (AICD) [39–41].

Immunologic and molecular aberrations

Cells within the CTCL tumour microenvironment display an exhausted phenotype, with upregulation of inhibitory immune checkpoints. Compared to healthy skin, both the presumably $CD4^+$ malignant T cells and the tumour-infiltrating $CD8^+$ T cells have shown increased expression of PD-1, CTLA-4, LAG3, and other immune checkpoints, with higher levels correlating to more advanced stage of disease [17]. Furthermore, differential expression of PD-1 in SS and MF has been demonstrated, with higher expression noted in malignant T cells of SS patients compared with MF patients, which may contribute to immunosuppression in SS [14]. KIR3DL2, a

member of the killer cell immunoglobulin (Ig)-like receptor (KIR), has also been demonstrated to have increased expression in SS, compared to non-transformed MF [42]. In a study of 33 SS patients, 32 (97.0%) showed positive expression of KIR3DL2. A previous study in 34 patients, conducted by the same group, found that 28 (82.4%) were positive for KIR3DL2. Of significance, expression of KIR3DL2 was not observed on phenotypically normal T cells. This data suggests that KIR3DL2 can be a positive marker for Sézary cells and, thus, could not only have utility in diagnosing SS, but also in monitoring during treatment [13].

The genetic basis for CTCL has not been fully elucidated. However, genomic analysis via comparative genomic hybridization (CGH) analysis, whole exome sequencing (WES), whole genome sequencing (WGS), and RNA-sequencing has revealed numerous cytogenetic abnormalities that provide insight into the pathogenesis of MF and SS. While the exact significance of these genetic alternations, including chromosomal imbalances (CIs), somatic copy number variants (SCNV), somatic single nucleotide variants (SSNV), and epigenetic modifications, is unknown, this data has potential therapeutic implications.

In a CGH analysis of 34 patients with CTCL, 18 of whom had SS, CIs were identified in 19 (55.9%) patients. The most frequent aberrations were losses involving chromosome 1p, 10q/10, and 19, and gains involving 4/4q, 18, and 17q/17. Apart from gains of chromosome 17q/17, which were only seen in SS, a similar pattern of CIs was seen in advanced MF and SS. Losses were more common in SS than in MF. Infrequent losses of chromosomes 6p, 13q, 16p/16, and 20, and gains of chromosome 8 were also observed in advanced MF and SS; and thus, may be indicative of disease progression [43]. A subsequent CGH analysis of 32 CTCL patients detected CIs in 21 (65.6%) patients, six of whom had stage III/IV (presumed E-MF and SS) disease. The most frequent aberrations were losses of chromosomal regions 17p, 13q, 10q, and 6q, and gains of chromatin of chromosome 7, 8q, and 17q11q22. Losses were, again, noted more abundant than gains in advanced CTCL. Importantly, the number of chromosomal aberrations correlated with clinical stage, which suggests that genes encoded on these loci may influence lymphomagenesis and disease progression [44].

Two comprehensive analyses studying 84 SS and 40 stage IV (presumed E-MF and SS) CTCL patients identified previously known chromosomal alterations, including gains of chromosome 8q and 17q and losses of chromosome 10q, 17p, and 19q; but also delved further to identify the target genes underlying the recurrent copy number mutations [45,46]. The former study, in addition to revealing recurrent genomic losses at 9p21.1 (CDKN2A), 10p11.22 (PTEN), and 13q14.2 (RB1), discovered genetic alterations in genes that have a role in epigenetic modification including chromatin and histone modification (i.e. ARID1A, ARID5B, MLL, MLL2, MLL4, SETD1A, SETD1B, SETD6) and DNA methylation (i.e. NCOR1, TET1, TET2, DNMT3A, DNMT3B) [46]. The latter study identified somatic mutations in 17 genes, implicating them in the pathogenesis of CTCL. These somatic mutations were demonstrated to have roles in T-cell signalling and differentiation (CD28 and CCR4), apoptotic pathways (FAS), NF-κB and STAT signalling pathways (STAT3 and STAT5B), the PI3K/AKT pathway (PTEN and RHOA), epigenetic regulation (ARID1A, DNMT3A, and KMT2C), cell cycle regulation (CDKN2A and RB), and regulation of genome integrity (TP53 and ATM) [45]. An additional analysis of 11 MF and SS patients noted recurrent alterations in TNFR2, as well as mutations in PI3K-related genes involved in TCR-CD28 signalling and mutations in NF-κB pathway genes [47].

Recent data has revealed that certain microRNAs (miRNAs) are differentially expressed in CTCL, and can distinguish CTCL from benign skin disease with 90–95% accuracy. Thus, these oncogenic (miR-21, miR-155, miR-326, miR-663b, and miR-711) and tumour suppressor (miR-203 and miR-205) miRNAs likely play a role in the pathogenesis of CTCL. While the aberrant expression of most of these miRNAs has not been associated with a specific stage of CTCL, miR-21 and miR-155, whose expression is mediated by JAK/STAT5, have demonstrated altered expression in SS and tumour stage MF, respectively [48]. Of note, an antagonist to miR-155 is currently being evaluated in a phase I/II clinical trial.

Treatment principles and regimen

The treatment of E-MF and SS is based on the extent of disease, patients' ages and comorbidities, and impact on quality of life. Current approaches for treating E-MF/SS include biologic, targeted, and immunotherapeutic therapies that can provide long term treatment with minimal side effects, while maintaining quality of life. None of these approaches are curative and, hence, patients frequently have relapses necessitating ongoing treatments. Standard regimens for E-MF and SS include extracorporeal photopheresis (ECP), subcutaneous interferon-α (IFN-α), oral bexarotene, histone deacetylase inhibitors (HDACis), and combinations using ECP with bexarotene and/or IFN-α (Table 1).

Biologic therapies

Extracorporeal photopheresis

ECP is a process in which leukocytes are withdrawn from the blood via apheresis, incubated with 8-methoxypsoralen (8-MOP) and exposed to UVA light (1–2 J/cm^2), then reinfused into the patient. ECP is empirically administered on two consecutive days every two to four weeks. While the immunomodulatory mechanisms that account for the efficacy of ECP have yet to be fully elucidated, current evidence supports the occurrence of two simultaneous and synergistic processes that stimulate a potent antitumor response. These processes are the induction of apoptosis in the circulating malignant T lymphocytes and the conversion of blood monocytes to immature dendritic cells (DCs). The immature DCs phagocytose the apoptotic malignant T lymphocytes and, subsequently, activate an antigen-specific immune response against the malignant T cell clone [49–51].

ECP was approved by the FDA in 1987 for the treatment of advanced CTCL following the preliminary results of a landmark, multicentre trial. The trial included a small cohort of refractory CTCL patients, in which 27 (73.0%) of 37 patients demonstrated partial or complete response, with a mean time to response (TTR) of 22.4 weeks. A greater response rate was noted in those with exfoliative erythroderma, as 24 (82.8%) of 29 responded to treatment, while only three (37.5%) of eight with stage I and II disease

Table 1
Therapies in erythrodermic mycosis fungoides and Sézary syndrome.

Treatment	Author	ORR	PR	CR	TTR (median)	DOR (median)	PFS (median)
Biologic therapies							
ECP							
-Monotherapy	Edelson et al [52]	73.0% (27/37); 82.8% (24/29) in exfoliative erythroderma			22.4 weeks (mean)		
-Combination with PUVA	Child et al [53]	56.5% (13/23) in SS					
Oral bexarotene							
-Monotherapy	Duvic et al [55]						
300 mg/m^2/d		44.6% (25/56); 36.4% (12/33) in E-MF/SS	42.9% (24/56)	1.8% (1/56)	25.7 weeks		
> 300 mg/m^2/d		55.3% (21/38)	42.1% (16/38)	13.2% (5/38)	8.4 weeks		
-Combination with denileukin diftitox	Foss et al [57]	66.7% (8/12)	33.3% (4/12)	33.3% (4/12)			
IFN-α							
-Monotherapy	Olsen et al [61]				8 weeks (mean)	14 weeks (mean)	
3 Mμ/d		37.5% (3/8)					
36 Mμ/d		78.6% (11/14)					
-Combination with PUVA	Kuzel et al [64]	89.7% (35/39); 85.7% (12/14) in E-MF/SS	28.2% (11/39); 35.7% (5/14) in E-MF/SS	61.5% (24/39); 50.0% (7/14) in E-MF/SS		28 months	
HDACi							
Vorinostat	Olsen et al [70]	29.7% (22/74); 33.3% (10/30) in SS	28.4% (21/74)	1.4% (1/74)	7.9 weeks; 8 weeks in SS	≥26.4 weeks in advanced CTCL	
Romidepsin	Whittaker et al [73]	34.4% (33/96); 32.4% (12/37) in E-MF/SS	28.1% (27/96); 27.0% (10/37) in E-MF/SS	6.3% (6/96); 5.4% (2/37) in E-MF/SS	2 months	15 months	
Panobinostat	Duvic et al [76]	17.3% (24/139)					
Bexarotene-exposed		15.2% (12/79); 28.6% (6/21) in SS	13.9% (11/79)	1.3% (1/79)	2.3 months	5.6 months	4.2 months
Bexarotene-naïve		20.0% (12/60); 16.7% (2/12) in SS	18.3% (11/60)	1.7% (1/60)	2.8 months	Not reached	3.7 months
Monoclonal antibodies							
Alemtuzumab (Only E-MF/SS)	Querfeld et al [82]	84.2% (16/19)	36.8% (7/19)	47.4% (9/19)	3 months	6 months	6 months
Mogamulizumab	Kim et al [90]	23.1% (43/186); 27.0% (10/37) in E-MF; 37.0% (30/81) in SS			3.3 months	25.5 months in blood; 20.6 months in skin; 15.5 months in LNs	6.7 months
Investigational therapies							
Durvalumab +/- lenalidomide	Querfeld et al [110]	ongoing					
TTI-621 (SIRPαFc)	Querfeld et al [116]	ongoing		16.7% (1/6)			
Anti-KIR3DL2 (IPH4102) (Only SS)	Bagot et al [117]	42.9% (15/35)	37.1% (13/35)	5.7% (2/35)	4.8 months	5.6 months	12.8 months
Antagomir-155 (MRG-106)	Querfeld et al [118]	95.8% (23/24)					

responded [52]. An RCT trial comparing psoralen with ultraviolet light A (PUVA) and ECP also demonstrated the ineffectiveness of ECP in treating plaque stage MF, but noted an overall response rate (ORR) of 56.5% in a group of 23 SS patients what were treated with ECP for at least six months. Response was positively correlated with Sézary cell count [53], though the opposite has been shown in other studies [16]. Subsequent studies with ECP used as monotherapy in MF and SS patients demonstrated ORRs of 52.9%–73.0% [51]. When ECP is used as part of combination therapy, especially with IFN-α, the ORRs have, in general, been higher than with ECP as monotherapy. ECP is well tolerated with few adverse events (AEs) noted. Most AEs were related to volume shifts (i.e. hypotension, exacerbation of congestive heart failure) or complications of venous access (i.e. venepuncture site hematoma, superficial thrombophlebitis, catheter-related sepsis) [16].

Oral bexarotene

Bexarotene (Targretin, LGD1069) is a synthetic retinoid that selectively activates retinoid-X receptors. It is an orally-administered medication that was approved by the FDA in 1999 for the treatment of all stages of CTCL. In vitro studies demonstrated that bexarotene functions via the induction of apoptosis in CTCL cell lines, though the precise mechanisms are unknown [54].

A multinational phase II/III trial of 94 patients with advanced MF and SS (stage IIB-IVB) demonstrated an ORR of 44.6% and 55.3% with daily doses of 300 mg/m^2 and > 300 mg/m^2, respectively. Median TTR was 25.7 weeks for doses of 300 mg/m^2/d and 8.4 weeks for doses > 300 mg/m^2/d. In 33 E-MF and SS (stage III and IV) patients, the ORR was 36.4% at a dose of 300 mg/m^2/d, with notable reduction in skin erythema and scaling. While there was a dose-relationship with regards to efficacy, a higher rate of AEs, most notably hyperlipidaemia, was also noted at doses > 300 mg/m^2/d when compared to doses of 300 mg/m^2/d. Thus, a starting dose of 300 mg/m^2/d demonstrated the best risk-benefit ratio [55].

The most common side effects of oral bexarotene therapy were hyperlipidaemia (hypertriglyceridemia more so than hypercholesterolemia), central hypothyroidism, and leukopenia, all of which were easily monitored with routine blood tests. Hypertriglyceridemia and hypercholesterolemia were managed with lipid lowering agents (LLA), and hypothyroidism was treated with thyroid supplementation. Hyperlipidaemia and hypothyroidism were noted to be reversible with discontinuation of bexarotene. Leukopenia had a low incidence, was mild, and responded to intervention with G-CSF [55,56].

A subsequent study in refractory, early and advanced CTCL with bexarotene used alone and in combination demonstrated improved clinical response rates when multiple LLAs were used to control dose-limiting hyperlipidaemia. For those treated with bexarotene alone, there was an ORR of 25.0%, 43.8%, and 90.0%, when treated with no LLA, one LLA, and two LLAs, respectively. When bexarotene was given in combination, ORRs of 66.7% and 75.0% were attained with use of one LLA and two LLAs, respectively. Of the 16 patients, 15 of whom had stage III/IV disease, treated with combination therapy, 11 (68.8%) responded, which included one CR. Of importance, it was noted that Gemfibrozil is contraindicated with use of bexarotene. Since bexarotene is metabolized by cytochrome P450 3A4, inhibition of this isoenzyme by Gemfibrozil results in increased plasma levels of bexarotene and triglycerides [56].

Bexarotene has been safely combined with PUVA, IFN-α, IFN-γ, and ECP, in patients with advanced, and/or refractory, CTCL [56]. A phase I study of bexarotene and denileukin diftitox exhibited a high ORR with an acceptable safety profile. 12 patients with relapsed or refractory CTCL, five of whom had stage III/IV disease, were treated with oral bexarotene administered by cohort dose-escalation at daily doses of 75, 150, 225, and 300 mg/day, and denileukin diftitox at a dose of 18 mcg/kg per day for three days per 21-day cycle. An ORR of 66.7% was reported with four PRs and four CRs. As with bexarotene alone, hypertriglyceridemia and hypothyroidism occurred in most patients and were managed with oral medication. Few grade III and IV AEs occurred [57]. The improved response rate of this combination therapy is likely related to the upregulation of functional high-affinity IL-2R subunits by bexarotene, which enhanced the cytotoxicity of the IL-2R-directed fusion toxin, denileukin diftitox [58].

Interferon-alpha

IFNs are endogenous cytokines that are part of the innate immune system. They exhibit pleiotropic cellular effects, including antiviral, antiproliferative, and immunomodulatory activity. IFN-α is a type I IFN with two subtypes, IFN-α-2a and IFN-α-2b, which share the same biologic activity. Recombinant IFN-α-2a and IFN-α-2b are commercially available as Roferon-A and Intron-A, respectively. However, Roferon-A, which is no longer available in the US, has been replaced by peg- IFN-α-2a (Pegasys). Type I IFNs mediate their effects, in part, via activation of the JAK/STAT signalling pathway, as well as by direct cytotoxic effects. Resistance to IFN-α has been associated with the loss of STAT1 expression [59].

The efficacy of IFN-α for the treatment of CTCL was first established in 1984. Heavily treated patients with advanced disease that were treated with 50 Mμ/m^2 IFN-α-2a three times per week (TIW) for at least three months demonstrated an ORR of 45% [60]. A subsequent trial in 22 early and advanced CTCL patients treated at doses of 3 and 36 Mμ daily of IFN-α-2a for 10 weeks showed an ORR of 37.5% and 78.6%, respectively; thus, demonstrating greater efficacy at higher doses. The mean TTR was eight weeks and mean duration of response (DOR) was 14 weeks. Of the six patients with stage III/IV disease, one CR was attained at low dose, and one CR and PR were attained at high dose [61]. While some patients on high dose required dose reduction, some on low dose were unable to achieve CR without dose escalation. Numerous other studies have shown that patients are better able to tolerate high doses of IFN-α when treated with dose escalation versus an initial high dose. The range of individually tolerated doses is between 3 and 18 Mμ daily. While there is no consensus on treatment regimen, a starting dose of 3 Mμ subcutaneously (SQ) daily is recommended, with gradual dose escalation [60].

The side effects can be acute or chronic, and are generally dose-related, though some may resolve or improve without a dose change. Side effects can also be mitigated by pre-treatment with acetaminophen or by administering injections at bedtime. Acute side effects of flu-like symptoms, including fever, chills, arthralgias, myalgias, and malaise, are experienced by most patients. Chronic side

effects include fatigue, anorexia, depression, diarrhoea, alopecia, hypothyroidism, chronic cough, myelosuppression, and impaired liver function [60,61].

Given the effectiveness of IFN-α as monotherapy, combination therapies were evaluated in an effort to extend its efficacy. IFN-α combined with PUVA was demonstrated to be superior to combinations with retinoids and ECP [62,63]. A phase II trial of 39 patients with early and advanced MF and SS used a combination of 12 Mμ TIW, SQ or intramuscularly, of IFN-α-2a, and PUVA TIW. An ORR of 89.7% was attained with 11 (28.2%) and 24 (61.5%) patients achieving a PR and CR, respectively. The median DOR was 28 months. In 14 patients with stage III/IV disease, an ORR of 85.7% was reached with five (35.7%) and seven (50.0%) patients achieving a PR and CR, respectively [64]. The mean ORR for 11 trials that investigated the combination of IFN-α and PUVA was 79% [62].

When compared to other types of treatments, especially chemotherapies and immunotherapies, IFN-α has a significant advantage in that there is no increased incidence of a second malignancy or cumulative dose effects, and rarely, drug-induced disorders. Thus, long-term use of IFN-α is safe and practical [60].

Histone deacetylase inhibitors

Histone modification via acetylation is a form of epigenetic gene modification that serves as an important regulatory mechanism for gene transcription. Histone acetylation and deacetylation exist in a dynamic equilibrium; however, this can be altered in malignancy [65,66]. Histone deacetylases (HDACs) are a class of ubiquitous enzymes that catalyse the removal of acetyl groups from histones, resulting in chromatin compaction. NCOR1 and CTBP1, genes that encode proteins involved in HDAC complexes, which regulate HDAC activity, have been found to have overexpression of mRNA in SS [67]. In cases of aberrant HDAC expression resulting in a neoplastic process, HDACis have been shown to inhibit cell growth, promote differentiation, and induce apoptosis [66,68], possibly by restoring the expression of tumour suppressor and/or cell cycle regulatory genes [69]. In targeting one or more of the 11 HDACs, HDACi also affect non-histone proteins whose activity is affected by acetylation, such as chromatin remodelling proteins, DNA-binding nuclear receptors, DNA repair enzymes, signalling mediators, structural proteins, transcription coregulators, and DNA-binding transcription factors [65]. HDACi have demonstrated a favourable side effect profile in phase II trials, and thus, are preferred over chemotherapies [66].

Vorinostat

Vorinostat (suberoylanilide [SAHA], Zolinza) is an orally administered, small-molecule competitive inhibitor of class I and II HDACs. It was approved by the FDA in 2006 for use in CTCL patients with at least stage IB disease that is progressive, persistent, or recurrent during or after treatment with at least two systemic therapies.

One phase II trial treated 74 patients with 400 mg daily, with dose adjustments made for grade III or IV toxicities. The 400-mg dose was generally well tolerated with only nine patients requiring one dose modification, and two requiring a second dose modification. The ORR was 29.7%, with one CR attained. Median TTR was 7.9 weeks. 10 (33.3%) of 30 patients with SS responded, with a median TTR of eight weeks. Additionally, pruritus relief was notable in both responders and non-responders with 21 (32.3%) of 65 patients with a score of at least three out of 10 endorsing improvement. Of those with severe pruritus, scores of at least seven out of 10, 13 (43.3%) of 30 had improvement, including five (31.3%) of 16 SS patients. Pruritus relief was achieved early and often sustained for the duration of treatment [70].

Another phase II trial utilized three separate dosing regimens, which are as follows: 400 mg daily; 300 mg twice daily, three days per week for four weeks, then, if tolerated, increased to five days per week; and induction with 300 mg twice daily for 14 days, with seven days off, then resumption of therapy at 200 mg twice daily. As in the previous trial, dosing modifications were made, as necessary, for grade III and IV toxicities, and were required in three patients, one from each treatment group. PR was achieved in eight (24.2%) of 33 patients, which was especially notable given the heavily pre-treated population. No CR was attained. The two discontinuous dosing regimens were demonstrated to have higher toxicity with no additional clinical benefit when compared to the continuous dosing of 400 mg daily. Again, rapid and persistent pruritus relief was demonstrated in responders and non-responders. 14 (45.2%) of 31 patients with baseline pruritus noted improvement, with the majority being in the continuous treatment group [71].

In both studies, Vorinostat demonstrated a favourable safety profile. The most common serious toxicities (grade III and IV) were dehydration, thrombocytopenia, nausea/vomiting, anaemia, hypotension, infection, sepsis, and pulmonary embolism. Importantly, toxicities were noted to be reversible with discontinuation of therapy [70–72].

Romidepsin

Romidepsin (FK228, depsipeptide, Istodax) is a potent, class I and II HDACi. It was approved by the FDA in 2009 for use in CTCL patients who received at least one prior systemic therapy. It is administered intravenously (IV) as a four-hour infusion of 14 mg/m^2, once a week for three weeks, with one week off. Treatment may be continued until the patient becomes intolerant to therapy or has disease progression.

A pivotal, phase II study of 96 patients demonstrated an ORR of 34.4%, with six complete responses. The median TTR was two months, and the median DOR was 15 months. In patients with blood involvement, either B1 or B2, 12 (32.4%) of 37 had a response, with two achieving CR. This response was noted to be rapid and sustained via assessment of Sézary cell counts. Relief of pruritus was significant with 60 (92.3%) of 65 patients with moderate to severe pruritus endorsing improvement. However, as with Vorinostat, relief of pruritus did not correlate with clinical response to treatment, as improvement was demonstrated in responders and non-responders [73].

Most toxicities reported were mild (grade I or II), the most common of which were GI disturbances (i.e. nausea, vomiting,

diarrhoea), fatigue, anorexia, and hematologic abnormalities (i.e. thrombocytopenia, anaemia). Additionally, as reported in phase I studies, ECG changes, though mild and clinically insignificant, were demonstrated. QTc prolongation was found to be independent of, but exacerbated by, anti-emetic therapy [73,74].

Panobinostat

Panobinostat (LBH589) is a potent, pan-HDACi that, in preclinical studies, has been demonstrated to induce apoptosis and inhibit cell proliferation [68]. In a phase I trial of 10 CTCL patients with advanced, refractory disease, panobinostat exhibited efficacy with four patients achieving a PR and two reaching a CR. Skin biopsies were evaluated via gene expression profiling, revealing the induction of transcriptional repression of genes, more so than activation, in treated patients. Specifically, genes involved in the regulation of cell cycle progression and angiogenesis were found to be downregulated [68,75].

A multicentre, phase II study evaluated MF/SS patients that had failed at least two prior systemic therapies, and stratified them based on prior exposure to bexarotene. Panobinostat was orally administered at 20 mg on Monday, Wednesday, and Friday each week on a 28-day cycle; and treatment continued until progression, intolerance, or discontinuation. In the primary analysis, an ORR of 17.3% was achieved for all patients, with responses reported in 12 (15.2%) of 79 bexarotene-exposed patients and 12 (20.0%) of 60 bexarotene-naïve patients, including one CR in each group. Of the SS patients, responses were observed in six (28.6%) of 21 and two (16.7%) of 12 in the bexarotene-exposed and bexarotene-naïve groups, respectively. The median progression-free survival (PFS) in the bexarotene-exposed and -naïve groups was 4.2 and 3.7 months, respectively. Some pruritus relief was experienced by 24 (24.7%) of the 97 patients with baseline pruritus. The most common AEs were thrombocytopenia, diarrhoea, fatigue, nausea, and poor appetite [76].

Monoclonal antibodies

Monoclonal antibodies (mAbs) augment the immune response to malignancy by selectively targeting tumour cells. MAbs mediate antitumor activity via three main immune effector mechanisms: antibody dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), and induction of adaptive immune responses [77,78].

Alemtuzumab

Alemtuzumab (Campath-1H) is a humanized IgG1 mAb targeting CD52, a cell surface antigen present on normal and malignant B cells and T cells. Its primary antitumor effect is thought to be via ADCC mediated by neutrophils and, less so, natural killer (NK) cells [12]. It is FDA-approved for the treatment of chronic lymphocytic leukaemia (CLL), and has shown benefit in the treatment of leukaemic CTCL, with erythroderma as a positive predictor of response [79].

Early studies in advanced, refractory or relapsed CTCL demonstrated good response with ORR, PR, and CR ranging from 51 to 84%, 23–37%, and 18–47%, respectively [80–82]. Benefit was greatest in those with erythrodermic MF and SS, possibly due to selective depletion of central memory T cells [12]. Most significant toxicities were hematologic (e.g. profound lymphopenia), potentially requiring granulocyte-colony stimulating factor (G-CSF), and infectious, including reactivation of CMV and herpes zoster, tuberculosis, and fungal infections. Given the risk of opportunistic infections, patients are maintained on prophylactic antibiotic and antiviral therapy, which has reduced, but not eliminated infectious complications [81,83]. While these early studies treated with doses of up to 30 mg TIW, SQ or IV, subsequent studies demonstrated that lower doses, typically 10 mg TIW, may be as efficacious with fewer infectious risks [12,84].

Mogamulizumab

Mogamulizumab (KW-0761, Poteligeo) is a humanized IgG1 mAb that selectively binds CC-chemokine receptor 4 (CCR4). It has an artificially defucosylated Fc region, which binds with high-affinity to the Fc receptor on effector cells to enhance ADCC. CCR4 is expressed on memory helper T cells and regulatory T cells (Tregs), and is involved in the trafficking of lymphocytes to the skin. CCR4 + tumour cells have been consistently demonstrated in various T cell malignancies such as CTCL, peripheral T cell lymphoma (PTCL) and adult T cell leukaemia/lymphoma (ATLL), and are significantly associated with poor prognosis [85–87].

A multicentre phase I/II trial in the U.S. demonstrated effectiveness in CTCL with an ORR of 36.8%, and a median PFS of 11.4 months. Of the 17 SS patients, six (35.5%) achieved PR, and two (11.8%) obtained CR [88]. A phase II trial in Japan demonstrated similar results in a small cohort of CTCL patients, achieving an ORR of 37.5% [89]. While mogamulizumab had been approved for use in ATLL in Japan since 2012, it was not approved for use in CTCL and PTCL until 2014 [85]. In the U.S., mogamulizumab just recently received FDA approval in September 2018, based on the findings of the MAVORIC trial, for use in relapsed or refractory MF and SS following at least one prior systemic therapy.

The MAVORIC trial was an international, phase III, randomized controlled trial that compared mogamulizumab, dosed at 1.0 mg/kg IV, weekly for the first 28-day cycle, then biweekly, with vorinostat, dosed at 400 mg orally, daily. Mogamulizumab demonstrated superiority to vorinostat in both ORR and median PFS, which was 23.1% and 6.7 months, respectively, in the mogamulizumab group, and 3.8% and 3.8 months, respectively, in the vorinostat group. Additionally, of the 133 patients that crossed over from vorinostat to mogamulizumab, 41 (30.8%) achieved an overall response. The effects of mogamulizumab were most pronounced in the blood with a median DOR of 25.5 months, compared to 20.6 months and 15.5 months in the skin and lymph nodes, respectively. Of the 81 SS patients in the mogamulizumab group, 30 (37.0%) had an overall response. The most common AEs in the mogamulizumab group were infusion-related reactions (34%), drug rash (24%), diarrhoea (24%), and fatigue (24%). Grade III and IV AEs of any cause were consistent between the two groups at 41%; and the most frequently reported treatment-related, serious AEs in the mogamulizumab

group were pneumonia (2%) and pyrexia (2%) [90].

Allogeneic stem cell transplant

Allogeneic stem cell transplant (SCT) is, currently, the only potential curative treatment for CTCL. While autologous SCT has demonstrated curative potential in Hodgkin lymphoma and various types of non-Hodgkin lymphoma, it is not recommended for the treatment of CTCL. Limited studies of autologous SCT, either from bone marrow or peripheral blood, preceded by high-dose combination chemotherapy with or without radiotherapy, yielded discouraging results in CTCL patients [91,92]. While an excellent ORR was achieved, with nearly all patients attaining CR, relapse occurred frequently and was often rapid. The median estimated time to disease progression across all studies was a paltry 2.3 months [93]. Furthermore, meta-analysis revealed superior overall survival rates and event free survival rates in allogeneic SCT over autologous SCT [94]. Allogeneic SCT has been demonstrated to achieve long-term remissions in refractory or relapsed CTCL, with PFS as high as 34% at 10 years [95]. Decreased relapse rates are thought to be attributable to a beneficial donor immune response directed against tumour cells, known as a graft-versus-lymphoma (GVL) effect [94,96]. However, this effect may be diminished in patients with large cell transformation [97,98].

Still, regardless of the use of myeloablative conditioning (MAC) or reduced intensity conditioning (RIC) regimen, relapse rates and transplant-related mortality rates with allogeneic SCT are substantial. Aside from disease progression, infection and complications from graft-versus-host-disease (GVHD) are the most common causes of death [95]. Yet, while there is minimal consensus on conditioning regimen, though RIC is favoured, the use of TSEBT as a debulking agent prior to conditioning may decreased rates of cutaneous GVHD [99,100]. Relapse rates have been shown to be independently affected by disease status prior to SCT [93,97,101]. Thus, attainment of CR or, at the very least, good PR is preferable prior to SCT, as GVL effect renders complete T cell depletion unnecessary [95]. Additionally, the optimal timing of transplant has not been completely outlined; though early consultation in transplant eligible patients is important as a prolonged time interval between diagnosis and transplant negatively influences outcomes [93,102].

While allogeneic SCT is an appropriate therapeutic option for refractory or relapsed MF/SS, as it induces durable responses with acceptable side-effects, the performance of genetically randomized control trials would be of benefit to properly assess the role of allogeneic SCT in the treatment of advanced CTCL [103].

Investigational therapies

Immune checkpoint inhibitors

Immune checkpoints modulate and quell the immune response in order to maintain self-tolerance and mitigate excessive tissue damage. Exploitation of these inhibitory immune checkpoints by tumour cells, via upregulation of immune checkpoints within the tumour microenvironment, provides a means for immune escape. Suppression of the antitumor response contributes to the persistence and progression of cancer. Thus, these immune checkpoints provide optimal therapeutic targets [104–106].

Durvalumab. Durvalumab is an inhibitor of the PD-1/PD-L1 immune checkpoint. It binds PD-L1, preventing transmission of an inhibitory signal to tumour-infiltrating immune cells. This antagonism allows for the reactivation of $CD8^+$ T cells from an exhausted state [107,108]. Notably, it also results in enhanced macrophage-mediated phagocytosis, as tumour associated macrophages in CTCL have been demonstrated to express PD-1 [17]. As with TTI-621, macrophage function is further augmented via ADCP [108]. Numerous trials with PD-1 and PD-L1 inhibitors have demonstrated increased antitumor activity in a variety of malignancies, but with fewer AEs noted with PD-L1 inhibitors [109]. Preliminary data from a phase I trial of durvalumab (1500 mg every four weeks) Vin patients with advanced CTCL have demonstrated significant clinical activity. Responses were durable and ongoing, and treatment was well tolerated with a low toxicity profile. Clinical response correlated with detectable levels of PD-L1 and nanoscale clusters of PD-1 in T cells [110].

TTI-621 (SIRPαFc). TTI-621 (SIRPαFc) is a novel immune checkpoint inhibitor that targets CD47, a ubiquitous antiphagocytic receptor, known commonly as the “do not eat” signal. It is a fully human recombinant fusion protein that consists of a SIRPα domain linked to an IgG1 Fc region, with the former engaging CD47 as a decoy receptor and the latter engaging the Fcγ receptor on macrophages. In effect, not only does TTI-621 prevent suppression of macrophage-mediated phagocytosis, it actually enhances macrophage function via antibody-dependent cellular phagocytosis (ADCP). The adaptive immune response is also augmented via increased tumour antigen presentation, promoting a tumour-specific $CD8^+$ T-cell response [108,111,112].

CD47 has been found to be upregulated on tumour cells in a multitude of malignancies, in an attempt to evade antitumor immunity. This increased expression of CD47 has been associated with worse prognosis in nearly all hematologic and solid tumour cancers [113,114]. Previous studies using TTI-621 have demonstrated a positive response to treatment, with increased anti-tumour activity across a broad range of cancers [112,115]. Preliminary data from a phase I trial of TTI-621, administered intralesionally, in patients with relapsed or refractory MF and SS demonstrate a reduction in disease burden across all patients, with one achieving CR, suggesting that CTCL is highly responsive to treatment [116].

Anti-KIR3DL2 (IPH4102)

Killer cell Ig-like receptor 3DL2 (KIR3DL2) is a transmembrane glycoprotein that belongs to the KIR family and is expressed on subsets of normal NK, $CD4^+$, and $CD8^+$ T cells. Studies have demonstrated expression of KIR3DL2 in all types of CTCL, and most

notably, in all stages of MF/SS, but with SS and transformed MF having the highest prevalence of expression. IPH4102 is a first-in-class anti-KIR3DL2 mAb that selectively depletes KIR3DL2-expressing cells via ADCC and ADCP, and demonstrated potent efficacy in preclinical models [42].

A recent multicentre, phase I trial evaluated IPH4102 in refractory CTCL patients that have failed at least two prior systemic therapies. IPH4102 was administered every week for four weeks, then every two weeks for 10 weeks, and then every four weeks until disease progression or toxicity. Results from a SS cohort of 35 patients are encouraging, demonstrating an ORR of 42.9% with two and 13 patients achieving CR and PR, respectively, and a median TTR of 4.8 months. Interestingly, those previously treated with Mogamulizumab had superior DOR and PFS. Marked improvement in pruritus, and overall quality of life, was demonstrated in patients that either responded to treatment or had stable disease. Most common AEs were asthenia (26%), peripheral oedema (26%), and fatigue (23%), which were grade I and II. Levels of KIR3DL2-expressing cells in the skin during treatment were predictive of best global response [117].

Antagomir-155 (MRG-106)

Antagomir-155 (MRG-106) is an oligonucleotide inhibitor of miR-155, an oncogenic miRNA overexpressed in CTCL. The efficacy of intralesional (IL), SQ, and IV administered antagomir-155 in patients with early and advanced MF is currently being evaluated in a national, dose-escalating, phase I/II clinical trial. Preliminary results revealed that 23 (95.8%) of 24 patients have shown improvement in either individually treated lesions (IL cohort) or total skin disease (SQ/IV cohorts) as measured by maximal change in CAILS or mSWAT. In the SQ/IV cohorts, nine (50.0%) of 18 patients reached a PR. In nine patients who received > 1 cycle of treatment, seven (77.8%) reached a PR, suggesting that longer duration of treatment may provide greater benefit. The drug was well tolerated with most AEs of grade I and II. A maximum tolerated dose has not been reached [118].

Supportive care

Patients with E-MF and SS are disabled by severe pruritus. Numerous medications, either alone or in combination, are used for symptom control, including antihistamines, gabapentin, pregabalin, aprepitant, and naloxone. Low-dose prednisone can be given for short-term symptom relief in cases of severe pruritus, but the course should be limited to avoid side effects of long-term steroid use. Regular bleach baths, according to guidelines by the Journal of the American Academy of Dermatology, are recommended to minimize bacterial colonization such as with S. aureus, which is known to drive clonal expansion of neoplastic T cells in the skin and increase the risk of secondary infections. Mild skin care using unscented, mild soaps and emollients is mandatory to improve pruritus, dryness, and scaling, and to keep skin barrier function intact.

Summary

MF is typically an indolent form of CTCL; however, SS and the erythrodermic type of MF represent aggressive variants. E-MF and SS commonly present a challenge for clinicians, both in terms of diagnosis and treatment. Clinicopathologic findings are often subtle and may mimic benign dermatoses. Thus, immunohistochemistry, molecular analysis, and blood flow cytometry are essential for accurate diagnosis. While the features of E-MF and SS are similar, with a hallmark of erythroderma, and varying numbers of Sézary cells in the blood, these rare forms of leukemic CTCL are considered two separate entities, arising from distinct cell populations. Distinguishing between E-MF and SS relies on determining the degree of blood involvement, based on the expanded criteria for B classification from the ISCL-EORTC. E-MF is defined by a low tumour burden (B0 and B1), whereas SS is defined by a high tumour burden (B2) with clonal rearrangement of TCR in the blood that is relevant to the clone in the skin. Recent studies have shown that PD-1 and KIR3DL2 have increased expression in advanced stages of MF/SS and may have a role as not only a diagnostic marker, but a means of monitoring treatment response. While microbiologic, viral, and environmental factors have been posited as causitive agents for the development of CTCL, no definitive cause is known. Recent genomic analyses in CTCL cell lines have revealed chromosomal, genetic, and epigenetic aberrations that may influence lymphomagenesis and disease progression. Treatment for E-MF and SS is guided by extent of disease, patients' ages and comorbidities, and side effect profile, as quality of life is an important aspect to balance with management of disease. Standard treatment options include biologic therapies, epigenetic modifiers, and monoclonal antibodies, with some demonstrating increased efficacy in combination. Investigational therapies have demonstrated promising results in early clinical trials. Proper skin care is also an essential component of disease managment.

Practice points

- E-CTCL encompasses E-MF and SS, leukaemic variants of CTCL that are distinguished by degree of blood involvement.
- E-MF and SS have overlapping clinical features, but are two distinct entities that arise from different memory T cell subsets.
- Immunohistochemistry, molecular analysis, and blood flow cytometry are essential for accurate diagnosis, as clinicopathologic findings may be subtle.
- PD-1 and KIR3DL2 have demonstrated differential expression with stage of MF/SS and, in addition to being a therapeutic target, may represent a diagnostic marker and means of tracking therapeutic efficacy.
- ECP and IFN-α, alone and in combination with PUVA, have demonstrated excellent response rates with great tolerability.
- IFN-α has many advantages including self-administration and low risk of toxicity, additional malignancy, or secondary disorder with long-term use.

- Romidepsin has exhibited favourable response rates with good duration of response.
- Alemtuzumab and mogamulizumab both exhibit good efficacy in the treatment of E-MF/SS with comparable PFS; but alemtuzumab has a higher response rate, while mogamulizumab has demonstrated an impressive duration of response in the blood.
- Allogeneic stem cell transplantation is currently the only potentially curative treatment option.
- Investigational therapies, including durvalumab, TTI-621, anti-KIR3DL2, and antagomir-155, have shown favourable outcomes in preliminary studies, and should be considered for any patient with relapsing or refractory disease.
- Management of symptoms, such as pruritus, is an essential component to treatment; as is proper skin care as bacterial colonization can be an instigator of disease flare.

Potential conflicts of interest

Xochiquetzal U. Martinez: None.

Cosimo Di Raimondo: None.

Farah R. Abdulla: Johnson & Johnson, Elorac, Trillium, Stemline, MiRagen, Bioniz, Mallinckrodt.

Jasmine Zain: Spectrum, Seattle Genetics.

Steven T. Rosen: Speaker's Bureau: Celgene, Global Education Group and Paradigm Medical Communications, LLC; Abbvie. Consulting: Novartis Pharmaceuticals Corporation, Pepromene Bio, Inc.; Exicure, Apobiologix/Apotex, Inc. EAB: Seattle Genetics, NeoGenomics, Aileron Therapeutics, Inc.

Christiane Querfeld: Advisory board: MiRagen, Kyowa Kirin, Medivir, Actelion, Seattle Genetics, Mallinckrodt. Investigator: Celgene, Seattle Genetics, MiRagen, Trillium, Bioniz, Elorac.

Acknowledgements

The above work was funded by the following: National Institutes of Health (NIH)/National Cancer Institute (NCI) Cancer Center Support Grant: P30CA033572 (Steven T. Rosen), and Leukemia Lymphoma Society Scholar Award: 2325-19 (Christiane Querfeld) .

References

[1] Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005 May 15;105(10):3768–85. PubMed PMID: 15692063.
[2] Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol : Off J Am Soc Clin Oncol 2010 Nov 1;28(31):4730–9. PubMed PMID: 20855822.
[3] Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood 2009 May 21;113(21):5064–73. PubMed PMID: 19279331. Pubmed Central PMCID: 2686177.
[4] Criscione VD, Weinstock MA. Incidence of cutaneous T-cell lymphoma in the United States, 1973-2002. Arch Dermatol 2007 Jul;143(7):854–9. PubMed PMID: 17638728.
[5] Korgavkar K, Xiong M, Weinstock M. Changing incidence trends of cutaneous T-cell lymphoma. JAMA Dermatol 2013 Nov;149(11):1295–9. PubMed PMID: 24005876.
[6] Wong HK, Mishra A, Hake T, Porcu P. Evolving insights in the pathogenesis and therapy of cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome). Br J Haematol 2011 Oct;155(2):150–66. PubMed PMID: 21883142. Pubmed Central PMCID: PMC4309373. Epub 2011/09/03.
[7] Willemze R, Cerroni L, Kempf W, Berti E, Facchetti F, Swerdlow SH, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood 2019 Jan;133(16):1703–14. PubMed PMID: 30635287.
[8] Vonderheid EC, Bernengo MG, Burg G, Duvic M, Heald P, Laroche L, et al. Update on erythrodermic cutaneous T-cell lymphoma: report of the international society for cutaneous lymphomas. J Am Acad Dermatol 2002 Jan;46(1):95–106. PubMed PMID: 11756953.
[9] Pulitzer M. Cutaneous T-cell lymphoma. Clin Lab Med 2017 Sep;37(3):527–46. PubMed PMID: 28802499. Pubmed Central PMCID: 5710803.
[10] Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. J Am Acad Dermatol 2014 Feb;70(2). 205 e1-16; quiz 21-2. PubMed PMID: 24438969.
[11] Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and sezary syndrome: a proposal of the international society for cutaneous lymphomas (ISCL) and the cutaneous lymphoma task force of the European organization of Research and treatment of cancer (EORTC). Blood 2007 Sep 15;110(6):1713–22. PubMed PMID: 17540844. Epub 2007/06/02.
[12] Clark RA, Watanabe R, Teague JE, Schlapbach C, Tawa MC, Adams N, et al. Skin effector memory T cells do not recirculate and provide immune protection in alemtuzumab-treated CTCL patients. Sci Transl Med 2012 Jan 18;4(117):117ra7. PubMed PMID: 22261031. Pubmed Central PMCID: 3373186.
[13] Bahler DW, Hartung L, Hill S, Bowen GM, Vonderheid EC. CD158k/KIR3DL2 is a useful marker for identifying neoplastic T-cells in Sezary syndrome by flow cytometry. Cytom B Clin Cytom 2008 May;74(3):156–62. PubMed PMID: 18061949.
[14] Cetinozman F, Jansen PM, Vermeer MH, Willemze R. Differential expression of programmed death-1 (PD-1) in Sezary syndrome and mycosis fungoides. Arch Dermatol 2012 Dec;148(12):1379–85. PubMed PMID: 23247480.
[15] Olsen EA. Evaluation, diagnosis, and staging of cutaneous lymphoma. Dermatol Clin 2015 Oct;33(4):643–54. PubMed PMID: 26433839.
[16] Olsen EA, Rook AH, Zic J, Kim Y, Porcu P, Querfeld C, et al. Sezary syndrome: immunopathogenesis, literature review of therapeutic options, and recommendations for therapy by the United States Cutaneous Lymphoma Consortium (USCLC). J Am Acad Dermatol 2011 Feb;64(2):352–404. PubMed PMID: 21145619. Epub 2010/12/15.
[17] Querfeld C, Leung S, Myskowski PL, Curran SA, Goldman DA, Heller G, et al. Primary T cells from cutaneous T-cell lymphoma skin explants display an exhausted immune checkpoint profile. Canc Immunol Res 2018 Aug;6(8):900–9. PubMed PMID: 29895574. Pubmed Central PMCID: 6074045.
[18] Diamandidou E, Cohen PR, Kurzrock R. Mycosis fungoides and Sezary syndrome. Blood 1996 Oct 1;88(7):2385–409. PubMed PMID: 8839829.
[19] Koh HK, Charif M, Weinstock MA. Epidemiology and clinical manifestations of cutaneous T-cell lymphoma. Hematol Oncol Clin N Am 1995 Oct;9(5):943–60. PubMed PMID: 8522490.
[20] Whittemore AS, Holly EA, Lee IM, Abel EA, Adams RM, Nickoloff BJ, et al. Mycosis fungoides in relation to environmental exposures and immune response: a case-control study. J Natl Cancer Inst 1989 Oct 18;81(20):1560–7. PubMed PMID: 2795681.
[21] Nickoloff BJ, Nestle FO, Zheng XG, Turka LA. T lymphocytes in skin lesions of psoriasis and mycosis fungoides express B7-1: a ligand for CD28. Blood 1994 May 1;83(9):2580–6. PubMed PMID: 7513205.

[22] Storz M, Zepter K, Kamarashev J, Dummer R, Burg G, Haffner AC. Coexpression of CD40 and CD40 ligand in cutaneous T-cell lymphoma (mycosis fungoides). Cancer Res 2001 Jan 15;61(2):452–4. PubMed PMID: 11212229.
[23] Jarrousse V, Quereux G, Marques-Briand S, Knol AC, Khammari A, Dreno B. Toll-like receptors 2, 4 and 9 expression in cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome). Eur J Dermatol : EJD 2006 Nov-Dec;16(6):636–41. PubMed PMID: 17229603.
[24] Yimin Kohanawa M, Zhao S, Ozaki M, Haga S, Nan G, et al. Contribution of toll-like receptor 2 to the innate response against Staphylococcus aureus infection in mice. PLoS One 2013;8(9). e74287. PubMed PMID: 24058538. Pubmed Central PMCID: 3772844.
[25] Talpur R, Bassett R, Duvic M. Prevalence and treatment of Staphylococcus aureus colonization in patients with mycosis fungoides and Sezary syndrome. Br J Dermatol 2008 Jul;159(1):105–12. PubMed PMID: 18489588.
[26] Tokura Y, Heald PW, Yan SL, Edelson RL. Stimulation of cutaneous T-cell lymphoma cells with superantigenic staphylococcal toxins. J Investig Dermatol 1992 Jan;98(1):33–7. PubMed PMID: 1728639.
[27] Herne KL, Talpur R, Breuer-McHam J, Champlin R, Duvic M. Cytomegalovirus seropositivity is significantly associated with mycosis fungoides and Sezary syndrome. Blood 2003 Mar 15;101(6):2132–6. PubMed PMID: 12446446.
[28] Pancake BA, Zucker-Franklin D, Coutavas EE. The cutaneous T cell lymphoma, mycosis fungoides, is a human T cell lymphotropic virus-associated disease. A study of 50 patients. J Clin Investig 1995 Feb;95(2):547–54. PubMed PMID: 7860737. Pubmed Central PMCID: 295510.
[29] Wood GS, Schaffer JM, Boni R, Dummer R, Burg G, Takeshita M, et al. No evidence of HTLV-I proviral integration in lymphoproliferative disorders associated with cutaneous T-cell lymphoma. Am J Pathol 1997 Feb;150(2):667–73. PubMed PMID: 9033279. Pubmed Central PMCID: 1858284.
[30] Ravat FE, Spittle MF, Russell-Jones R. Primary cutaneous T-cell lymphoma occurring after organ transplantation. J Am Acad Dermatol 2006 Apr;54(4):668–75. PubMed PMID: 16546591.
[31] Rodriguez-Gil Y, Palencia SI, Lopez-Rios F, Ortiz PL, Rodriguez-Peralto JL. Mycosis fungoides after solid-organ transplantation: report of 2 new cases. Am J Dermatopathol 2008 Apr;30(2):150–5. PubMed PMID: 18360119.
[32] Kaufman D, Gordon LI, Variakojis D, Caro WA, Marder R, Jumbelic M, et al. Successfully treated Hodgkin's disease followed by mycosis fungoides: case report and review of the literature. Cutis 1987 Apr;39(4):291–6. PubMed PMID: 3581901.
[33] Burns MK, Cooper KD. Cutaneous T-cell lymphoma associated with HIV infection. J Am Acad Dermatol 1993 Sep;29(3):394–9. PubMed PMID: 8349855.
[34] Wilkins K, Turner R, Dolev JC, LeBoit PE, Berger TG, Maurer TA. Cutaneous malignancy and human immunodeficiency virus disease. J Am Acad Dermatol 2006 Feb;54(2):189–206. quiz 7-10. PubMed PMID: 16443048.
[35] Adams AE, Zwicker J, Curiel C, Kadin ME, Falchuk KR, Drews R, et al. Aggressive cutaneous T-cell lymphomas after TNFalpha blockade. J Am Acad Dermatol 2004 Oct;51(4):660–2. PubMed PMID: 15389210.
[36] Dequidt L, Franck N, Sanchez-Pena P, Dalle S, Adamski H, Boulinguez S, et al. Cutaneous lymphomas appearing under biologics: 44 cases from the French study group on cutaneous lymphomas and French pharmacovigilance database. Br J Dermatol 2019 Mar. [epub ahead of print] PubMed PMID: 30835817.
[37] Hodak E, Lapidoth M, Kohn K, David D, Brautbar B, Kfir K, et al. Mycosis fungoides: HLA class II associations among Ashkenazi and non-Ashkenazi Jewish patients. Br J Dermatol 2001 Dec;145(6):974–80. PubMed PMID: 11899152.
[38] Jackow CM, McHam JB, Friss A, Alvear J, Reveille JR, Duvic M. HLA-DR5 and DQB1*03 class II alleles are associated with cutaneous T-cell lymphoma. J Investig Dermatol 1996 Sep;107(3):373–6. PubMed PMID: 8751973.
[39] Beyer M, Mobs M, Humme D, Sterry W. Pathogenesis of mycosis fungoides. Journal der Deutschen Dermatologischen Gesellschaft = J Ger Soc Dermatol : JDDG 2011 Aug;9(8):594–8. PubMed PMID: 21371258.
[40] Klemke CD, Brenner D, Weiss EM, Schmidt M, Leverkus M, Gulow K, et al. Lack of T-cell receptor-induced signaling is crucial for CD95 ligand up-regulation and protects cutaneous T-cell lymphoma cells from activation-induced cell death. Cancer Res 2009 May 15;69(10):4175–83. PubMed PMID: 19435902.
[41] Wilcox RA. Cutaneous T-cell lymphoma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol 2016 Jan;91(1):151–65. PubMed PMID: 26607183. Pubmed Central PMCID: 4715621.
[42] Bagot M, Porcu P, Ram-Wolff C, Khodadoust M, Battistella M, Marie-Cardine A, et al. First-in-Human, multicenter phase I study of IPH4102, first-in-class humanized anti-KIR3DL2 monoclonal antibody, in relapsed/refractory cutaneous T-cell lymphomas: preliminary safety, exploratory and clinical activity results. Blood 2016 Dec;128(22):7. PubMed PMID: WOS:000394452308018. English.
[43] Mao X, Lillington D, Scarisbrick JJ, Mitchell T, Czepulkowski B, Russell-Jones R, et al. Molecular cytogenetic analysis of cutaneous T-cell lymphomas: identification of common genetic alterations in Sezary syndrome and mycosis fungoides. Br J Dermatol 2002 Sep;147(3):464–75. PubMed PMID: 12207585. Epub 2002/09/05.
[44] Fischer TC, Gellrich S, Muche JM, Sherev T, Audring H, Neitzel H, et al. Genomic aberrations and survival in cutaneous T cell lymphomas. J Investig Dermatol 2004 Mar;122(3):579–86. PubMed PMID: 15086538. Epub 2004/04/17.
[45] Choi J, Goh G, Walradt T, Hong BS, Bunick CG, Chen K, et al. Genomic landscape of cutaneous T cell lymphoma. Nat Genet 2015 Sep;47(9):1011–9. PubMed PMID: 26192916. Pubmed Central PMCID: PMC4552614. Epub 2015/07/21.
[46] Kiel M, Sahasrabuddhe AA, Velusamy T, Chung F, Bailey NG, Betz BL, et al. Integrated genome sequencing reveals frequent loss of function alterations of ARID1A and other epigenetic modifiers in sezary syndrome. Blood 2014 Dec;124(21):3. PubMed PMID: WOS:000349242705136. English.
[47] Ungewickell A, Bhaduri A, Rios E, Reuter J, Lee CS, Mah A, et al. Genomic analysis of mycosis fungoides and Sezary syndrome identifies recurrent alterations in TNFR2. Nat Genet 2015 Sep;47(9):1056–60. PubMed PMID: 26258847. Pubmed Central PMCID: PMC6091217. Epub 2015/08/11.
[48] Ralfkiaer U, Hagedorn PH, Bangsgaard N, Lovendorf MB, Ahler CB, Svensson L, et al. Diagnostic microRNA profiling in cutaneous T-cell lymphoma (CTCL). Blood 2011 Nov 24;118(22):5891–900. PubMed PMID: 21865341. Pubmed Central PMCID: PMC3342856. Epub 2011/08/26.
[49] Duvic M, Chiao N, Talpur R. Extracorporeal photopheresis for the treatment of cutaneous T-cell lymphoma. J Cutan Med Surg 2003 Jul-Aug;7(4 Suppl):3–7. PubMed PMID: 12958700. Epub 2003/09/06.
[50] Maeda A, Schwarz A, Kernebeck K, Gross N, Aragane Y, Peritt D, et al. Intravenous infusion of syngeneic apoptotic cells by photopheresis induces antigen-specific regulatory T cells. J Immunol 2005 May 15;174(10):5968–76. PubMed PMID: 15879089. Epub 2005/05/10.
[51] Zic JA. The treatment of cutaneous T-cell lymphoma with photopheresis. Dermatol Ther 2003;16(4):337–46. PubMed PMID: 14686977. Epub 2003/12/23.
[52] Edelson R, Berger C, Gasparro F, Jegasothy B, Heald P, Wintroub B, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. N Engl J Med 1987 Feb 5;316(6):297–303. PubMed PMID: 3543674. Epub 1987/02/05.
[53] Child FJ, Mitchell TJ, Whittaker SJ, Scarisbrick JJ, Seed PT, Russell-Jones R. A randomized cross-over study to compare PUVA and extracorporeal photopheresis in the treatment of plaque stage (T2) mycosis fungoides. Clin Exp Dermatol 2004 May;29(3):231–6. PubMed PMID: 15115499. Epub 2004/04/30.
[54] Zhang C, Hazarika P, Ni X, Weidner DA, Duvic M. Induction of apoptosis by bexarotene in cutaneous T-cell lymphoma cells: relevance to mechanism of therapeutic action. Clin Cancer Res : Off J Am Assoc Canc Res 2002 May;8(5):1234–40. PubMed PMID: 12006543. Epub 2002/05/15.
[55] Duvic M, Hymes K, Heald P, Breneman D, Martin AG, Myskowski P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol : Off J Am Soc Clin Oncol 2001 May 1;19(9):2456–71. PubMed PMID: 11331325. Epub 2001/05/02.
[56] Talpur R, Ward S, Apisarnthanarax N, Breuer-Mcham J, Duvic M. Optimizing bexarotene therapy for cutaneous T-cell lymphoma. J Am Acad Dermatol 2002 Nov;47(5):672–84. PubMed PMID: 12399758. Epub 2002/10/26.
[57] Foss F, Demierre MF, DiVenuti G. A phase-1 trial of bexarotene and denileukin diftitox in patients with relapsed or refractory cutaneous T-cell lymphoma. Blood 2005 Jul 15;106(2):454–7. PubMed PMID: 15811959. Epub 2005/04/07.
[58] Gorgun G, Foss F. Immunomodulatory effects of RXR rexinoids: modulation of high-affinity IL-2R expression enhances susceptibility to denileukin diftitox. Blood 2002 Aug 15;100(4):1399–403. PubMed PMID: 12149223. Epub 2002/08/01.
[59] Sun WH, Pabon C, Alsayed Y, Huang PP, Jandeska S, Uddin S, et al. Interferon-alpha resistance in a cutaneous T-cell lymphoma cell line is associated with lack of STAT1 expression. Blood 1998 Jan 15;91(2):570–6. PubMed PMID: 9427711. Epub 1998/01/15.
[60] Olsen EA. Interferon in the treatment of cutaneous T-cell lymphoma. Dermatol Ther 2003;16(4):311–21. PubMed PMID: 14686974. Epub 2003/12/23.
[61] Olsen EA, Rosen ST, Vollmer RT, Variakojis D, Roenigk Jr. HH, Diab N, et al. Interferon alfa-2a in the treatment of cutaneous T cell lymphoma. J Am Acad

Dermatol 1989 Mar;20(3):395–407. PubMed PMID: 2783939. Epub 1989/03/01.
[62] Humme D, Nast A, Erdmann R, Vandersee S, Beyer M. Systematic review of combination therapies for mycosis fungoides. Cancer Treat Rev 2014 Sep;40(8):927–33. PubMed PMID: 24997678. Epub 2014/07/07.
[63] Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, Dummer R, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome - update 2017. Eur J Cancer 2017 May;77:57–74. PubMed PMID: 28365528. Epub 2017/04/04.
[64] Kuzel TM, Roenigk Jr. HH, Samuelson E, Herrmann JJ, Hurria A, Rademaker AW, et al. Effectiveness of interferon alfa-2a combined with phototherapy for mycosis fungoides and the Sezary syndrome. J Clin Oncol : Off J Am Soc Clin Oncol 1995 Jan;13(1):257–63. PubMed PMID: 7799028. Epub 1995/01/01.
[65] Eckschlager T, Plch J, Stiborova M, Hrabeta J. Histone deacetylase inhibitors as anticancer drugs. Int J Mol Sci 2017 Jul 1;18(7). PubMed PMID: 28671573. Pubmed Central PMCID: 5535906.
[66] Lopez AT, Bates S, Geskin L. Current status of HDAC inhibitors in cutaneous T-cell lymphoma. Am J Clin Dermatol 2018 Dec;19(6):805–19. PubMed PMID: 30173294.
[67] Izykowska K, Przybylski GK, Gand C, Braun FC, Grabarczyk P, Kuss AW, et al. Genetic rearrangements result in altered gene expression and novel fusion transcripts in Sezary syndrome. Oncotarget 2017 Jun 13;8(24):39627–39. PubMed PMID: 28489605. Pubmed Central PMCID: 5503638.
[68] Hymes KB. The role of histone deacetylase inhibitors in the treatment of patients with cutaneous T-cell lymphoma. Clin Lymphoma, Myeloma & Leukemia 2010 Apr;10(2):98–109. PubMed PMID: 20371442.
[69] Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome): part II. Prognosis, management, and future directions. J Am Acad Dermatol 2014 Feb;70(2). 223 e1-17; quiz 40-2. PubMed PMID: 24438970.
[70] Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol : Off J Am Soc Clin Oncol 2007 Jul 20;25(21):3109–15. PubMed PMID: 17577020.
[71] Duvic M, Talpur R, Ni X, Zhang C, Hazarika P, Kelly C, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007 Jan 1;109(1):31–9. PubMed PMID: 16960145. Pubmed Central PMCID: 1785068.
[72] Duvic M, Olsen EA, Breneman D, Pacheco TR, Parker S, Vonderheid EC, et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2009 Dec;9(6):412–6. PubMed PMID: 19951879.
[73] Whittaker SJ, Demierre MF, Kim EJ, Rook AH, Lerner A, Duvic M, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol : Off J Am Soc Clin Oncol 2010 Oct 10;28(29):4485–91. PubMed PMID: 20697094.
[74] Piekarz RL, Frye R, Turner M, Wright JJ, Allen SL, Kirschbaum MH, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. J Clin Oncol : Off J Am Soc Clin Oncol 2009 Nov 10;27(32):5410–7. PubMed PMID: 19826128. Pubmed Central PMCID: 2773225.
[75] Ellis L, Pan Y, Smyth GK, George DJ, McCormack C, Williams-Truax R, et al. Histone deacetylase inhibitor panobinostat induces clinical responses with associated alterations in gene expression profiles in cutaneous T-cell lymphoma. Clin Cancer Res : Off J Am Assoc Canc Res 2008 Jul 15;14(14):4500–10. PubMed PMID: 18628465.
[76] Duvic M, Dummer R, Becker JC, Poulalhon N, Ortiz Romero P, Grazia Bernengo M, et al. Panobinostat activity in both bexarotene-exposed and -naive patients with refractory cutaneous T-cell lymphoma: results of a phase II trial. Eur J Cancer 2013 Jan;49(2):386–94. PubMed PMID: 22981498.
[77] Adams GP, Weiner LM. Monoclonal antibody therapy of cancer. Nat Biotechnol 2005 Sep;23(9):1147–57. PubMed PMID: 16151408.
[78] Weiner LM, Surana R, Wang S. Monoclonal antibodies: versatile platforms for cancer immunotherapy. Nat Rev Immunol 2010 May;10(5):317–27. PubMed PMID: 20414205. Pubmed Central PMCID: 3508064.
[79] Watanabe R, Teague JE, Fisher DC, Kupper TS, Clark RA. Alemtuzumab therapy for leukemic cutaneous T-cell lymphoma: diffuse erythema as a positive predictor of complete remission. JAMA Dermatol 2014 Jul;150(7):776–9. PubMed PMID: 24760312. Pubmed Central PMCID: 4092049.
[80] de Masson A, Guitera P, Brice P, Moulonguet I, Mouly F, Bouaziz JD, et al. Long-term efficacy and safety of alemtuzumab in advanced primary cutaneous T-cell lymphomas. Br J Dermatol 2014 Mar;170(3):720–4. PubMed PMID: 24438061.
[81] Lundin J, Hagberg H, Repp R, Cavallin-Stahl E, Freden S, Juliusson G, et al. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. Blood 2003 Jun 1;101(11):4267–72. PubMed PMID: 12543862.
[82] Querfeld C, Mehta N, Rosen ST, Guitart J, Rademaker A, Gerami P, et al. Alemtuzumab for relapsed and refractory erythrodermic cutaneous T-cell lymphoma: a single institution experience from the Robert H. Lurie Comprehensive Cancer Center. Leuk Lymphoma 2009 Dec;50(12):1969–76. PubMed PMID: 19860617.
[83] Dearden CE, Matutes E, Catovsky D. Alemtuzumab in T-cell malignancies. Med Oncol 2002;19 Suppl:S27–32. PubMed PMID: 12180489.
[84] Bernengo MG, Quaglino P, Comessatti A, Ortoncelli M, Novelli M, Lisa F, et al. Low-dose intermittent alemtuzumab in the treatment of Sezary syndrome: clinical and immunologic findings in 14 patients. Haematologica 2007 Jun;92(6):784–94. PubMed PMID: 17550851.
[85] Duvic M, Evans M, Wang C. Mogamulizumab for the treatment of cutaneous T-cell lymphoma: recent advances and clinical potential. Ther Adv Hematol 2016 Jun;7(3):171–4. PubMed PMID: 27247757. Pubmed Central PMCID: 4872175.
[86] Ishida T, Iida S, Akatsuka Y, Ishii T, Miyazaki M, Komatsu H, et al. The CC chemokine receptor 4 as a novel specific molecular target for immunotherapy in adult T-Cell leukemia/lymphoma. Clin Cancer Res : Off J Am Assoc Canc Res 2004 Nov 15;10(22):7529–39. PubMed PMID: 15569983.
[87] Ishida T, Inagaki H, Utsunomiya A, Takatsuka Y, Komatsu H, Iida S, et al. CXC chemokine receptor 3 and CC chemokine receptor 4 expression in T-cell and NK-cell lymphomas with special reference to clinicopathological significance for peripheral T-cell lymphoma, unspecified. Clin Cancer Res : Off J Am Assoc Canc Res 2004 Aug 15;10(16):5494–500. PubMed PMID: 15328188.
[88] Duvic M, Pinter-Brown LC, Foss FM, Sokol L, Jorgensen JL, Challagundla P, et al. Phase 1/2 study of mogamulizumab, a defucosylated anti-CCR4 antibody, in previously treated patients with cutaneous T-cell lymphoma. Blood 2015 Mar 19;125(12):1883–9. PubMed PMID: 25605368. Pubmed Central PMCID: 4375715.
[89] Ogura M, Ishida T, Hatake K, Taniwaki M, Ando K, Tobinai K, et al. Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-cc chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma. J Clin Oncol : Off J Am Soc Clin Oncol 2014 Apr 10;32(11):1157–63. PubMed PMID: 24616310.
[90] Kim YH, Bagot M, Pinter-Brown L, Rook AH, Porcu P, Horwitz SM, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol 2018 Sep;19(9):1192–204. PubMed PMID: 30100375.
[91] Bigler RD, Crilley P, Micaily B, Brady LW, Topolsky D, Bulova S, et al. Autologous bone marrow transplantation for advanced stage mycosis fungoides. Bone Marrow Transplant 1991 Feb;7(2):133–7. PubMed PMID: 2049557.
[92] Russell-Jones R, Child F, Olavarria E, Whittaker S, Spittle M, Apperley J. Autologous peripheral blood stem cell transplantation in tumor-stage mycosis fungoides: predictors of disease-free survival. Ann N Y Acad Sci 2001 Sep;941:147–54. PubMed PMID: 11594568.
[93] Duarte RF, Schmitz N, Servitje O, Sureda A. Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. Bone Marrow Transplant 2008;41:597. 01/07/online.
[94] Wu PA, Kim YH, Lavori PW, Hoppe RT, Stockerl-Goldstein KE. A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. Biol Blood Marrow Transplant : J Am Soc Blood Marrow Transplant 2009 Aug;15(8):982–90. PubMed PMID: 19589488. Pubmed Central PMCID: 6402786.
[95] Johnson WT, Mukherji R, Kartan S, Nikbakht N, Porcu P, Alpdogan O. Allogeneic hematopoietic stem cell transplantation in advanced stage mycosis fungoides and Sezary syndrome: a concise review. Chin Clin Oncol 2019 Feb;8(1):12. PubMed PMID: 30525754.
[96] Oyama Y, Guitart J, Kuzel TM, Burt RK, Rosen ST. High-dose therapy and bone marrow transplantation in cutaneous T-cell lymphoma. Hematol Oncol Clin N Am 2003 Dec;17(6):1475–83. xi. PubMed PMID: 14710898.
[97] de Masson A, Beylot-Barry M, Bouaziz JD, Peffault de Latour R, Aubin F, Garciaz S, et al. Allogeneic stem cell transplantation for advanced cutaneous T-cell lymphomas: a study from the French society of bone marrow transplantation and French study group on cutaneous lymphomas. Haematologica 2014 Mar;99(3):527–34. PubMed PMID: 24213148. Pubmed Central PMCID: 3943317.
[98] Herbert KE, Spencer A, Grigg A, Ryan G, McCormack C, Prince HM. Graft-versus-lymphoma effect in refractory cutaneous T-cell lymphoma after reduced-

intensity HLA-matched sibling allogeneic stem cell transplantation. Bone Marrow Transplant 2004 Sep;34(6):521–5. PubMed PMID: 15286686.
[99] Duvic M, Donato M, Dabaja B, Richmond H, Singh L, Wei W, et al. Total skin electron beam and non-myeloablative allogeneic hematopoietic stem-cell transplantation in advanced mycosis fungoides and Sezary syndrome. J Clin Oncol : Off J Am Soc Clin Oncol 2010 May 10;28(14):2365–72. PubMed PMID: 20351328.
[100] Hosing C, Bassett R, Dabaja B, Talpur R, Alousi A, Ciurea S, et al. Allogeneic stem-cell transplantation in patients with cutaneous lymphoma: updated results from a single institution. Ann Oncol : Off J Eur Soc Med Oncol 2015 Dec;26(12):2490–5. PubMed PMID: 26416896. Pubmed Central PMCID: 4855245.
[101] Atilla E, Atilla PA, Bozdag SC, Yuksel MK, Toprak SK, Topcuoglu P, et al. Allogeneic hematopoietic stem cell transplantation for refractory mycosis fungoides (MF) and Sezary syndrome (SS). Int J Hematol 2017 Sep;106(3):426–30. PubMed PMID: 28466385.
[102] Cudillo L, Cerretti R, Picardi A, Mariotti B, De Angelis G, Cantonetti M, et al. Allogeneic hematopoietic stem cell transplantation in primary cutaneous T cell lymphoma. Ann Hematol 2018 Jun;97(6):1041–8. PubMed PMID: 29442161.
[103] Schlaak M, Pickenhain J, Theurich S, Skoetz N, von Bergwelt-Baildon M, Kurschat P. Allogeneic stem cell transplantation versus conventional therapy for advanced primary cutaneous T-cell lymphoma. Cochrane Database Syst Rev 2013 Aug 29(8):CD008908. PubMed PMID: 23986525.
[104] La-Beck NM, Jean GW, Huynh C, Alzghari SK, Lowe DB. Immune checkpoint inhibitors: new insights and current place in cancer therapy. Pharmacotherapy 2015 Oct;35(10):963–76. PubMed PMID: 26497482.
[105] Mahoney KM, Atkins MB. Prognostic and predictive markers for the new immunotherapies. Oncology 2014 Nov;28(Suppl 3):39–48. PubMed PMID: 25384886.
[106] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Canc 2012 Mar 22;12(4):252–64. PubMed PMID: 22437870. Pubmed Central PMCID: 4856023.
[107] Gordon SR, Maute RL, Dulken BW, Hutter G, George BM, McCracken MN, et al. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. Nature 2017 May 25;545(7655):495–9. PubMed PMID: 28514441. Pubmed Central PMCID: 5931375.
[108] Sockolosky JT, Dougan M, Ingram JR, Ho CC, Kauke MJ, Almo SC, et al. Durable antitumor responses to CD47 blockade require adaptive immune stimulation. Proc Natl Acad Sci USA 2016 May 10;113(19):E2646–54. PubMed PMID: 27091975. Pubmed Central PMCID: 4868409.
[109] Kim JW, Eder JP. Prospects for targeting PD-1 and PD-L1 in various tumor types. Oncology 2014 Nov;28(Suppl 3):15–28. PubMed PMID: 25387682.
[110] Querfeld C, Zain JM, Wakefield DL, Jovanovic-Talisman T, Kil SH, Estephan R, et al. Phase 1/2 trial of durvalumab and lenalidomide in patients with cutaneous T cell lymphoma (CTCL): preliminary results of phase I results and correlative studies. Blood 2018 Nov 29:132. PubMed PMID: WOS:000454842800123.
[111] Dheilly E, Majocchi S, Moine V, Didelot G, Broyer L, Calloud S, et al. Tumor-directed blockade of CD47 with bispecific antibodies induces adaptive antitumor immunity. Antibodies 2018;7(1):3. https://doi.org/10.3390/antib7010003. PubMed PMID.
[112] Petrova PS, Viller NN, Wong M, Pang X, Lin GH, Dodge K, et al. TTI-621 (SIRPalphaFc): a CD47-blocking innate immune checkpoint inhibitor with broad antitumor activity and minimal erythrocyte binding. Clin Cancer Res : Off J Am Assoc Canc Res 2017 Feb 15;23(4):1068–79. PubMed PMID: 27856600.
[113] Chao MP, Weissman IL, Majeti R. The CD47-SIRPalpha pathway in cancer immune evasion and potential therapeutic implications. Curr Opin Immunol 2012 Apr;24(2):225–32. PubMed PMID: 22310103. Pubmed Central PMCID: 3319521.
[114] Weiskopf K. Cancer immunotherapy targeting the CD47/SIRPalpha axis. Eur J Cancer 2017 May;76:100–9. PubMed PMID: 28286286.
[115] Ansell SM, Chen RW, Flinn I, Maris MB, O'Connor OA, Wieland E, et al. A phase 1 study of TTI-621, a novel immune checkpoint inhibitor targeting CD47, in subjects with relapsed or refractory hematologic malignancies. J Clin Oncol 2016 May 20;34(15). PubMed PMID: WOS:000404711505097.
[116] Querfeld C, Thompson J, Taylor M, Pillai R, Johnson LDS, Catalano T, et al. A single direct intratumoral injection of TTI-621 (SIRP alpha Fc) induces antitumor activity in patients with relapsed/refractory mycosis fungoides and sezary syndrome: preliminary findings employing an immune checkpoint inhibitor blocking the CD47 "do not eat. Signal Blood 2017 Dec 7:130. PubMed PMID: WOS:000432419703087.
[117] Bagot M, Porcu P, William BM, Battistella M, Vermeer M, Whittaker S, et al. IPH4102; an anti-KIR3DL2 monoclonal antibody in refractory sezary syndrome: results from a multicenter phase 1 trial. Blood 2018 Nov 29:132. PubMed PMID: WOS:000454837602062.
[118] Querfeld C, Foss FM, Pinter-Brown LC, Porcu P, William BM, Pacheco T, et al. Phase 1 study of the safety and efficacy of MRG-106, a synthetic inhibitor of microRNA-155, in CTCL patients. Blood 2017 Dec;130:3. PubMed PMID: WOS:000432419402070. English.