Curr Hematol Malig Rep (2015) 10:468–476
DOI 10.1007/s11899-015-0293-y

Cutaneous T cell Lymphoma: an Update on Pathogenesis and Systemic Therapy

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Published online: 1 December 2015

Abstract Mycosis fungoides (MF) and its leukemic variant, Sézary syndrome (SS), are malignancies of skin-homing T cells that comprise the majority of cutaneous T cell lymphomas (CTCL). Treatment of CTCL is limited and can be approached by skin-directed therapy or systemic therapy. Recent investigations into the pathogenesis of MF and SS have broadened the therapeutic targets; here, we review emerging concepts in the pathogenesis of MF and SS as well as novel and traditional systemic therapies for MF and SS. These include histone deacetylase inhibitors (vorinostat, romidepsin, panobinostat, and belinostat), monoclonal antibodies (alemtuzumab, brentuximab vedotin, and mogamulizumab) and single-agent cytotoxic chemotherapeutic agents (e.g., pralatrexate, doxorubicin, bendamustine, and forodesine), as well as multi-agent chemotherapy regimens.

Keywords Cutaneous T cell lymphoma · Pathogenesis · Chemotherapy · Monoclonal antibodies

Abbreviations

CTCL	Cutaneous T cell lymphoma
L-CTCL	Leukemic CTCL
MF	Mycosis fungoides
T_{CM}	Central memory T cell
T_{EM}	Effector memory T cell
HDAC	Histone deacetylase
DAC	Deacetylase
FDA	Food and Drug Administration
PTCL	Peripheral T cell lymphoma
ORR	Overall response rate
GI	Gastrointestinal
IV	Intravenous
CR	Complete response
PR	Partial response
CLL	Chronic lymphocytic leukemia
SC	Subcutaneous
ALCL	Anaplastic large cell lymphoma
PDX	Pralatrexate
MTX	Methotrexate
IFN	Interferon

Introduction

Cutaneous T cell lymphoma (CTCL) is a group of heterogeneous non-Hodgkin lymphomas that represent malignancies of skin-homing T cells [1] where mycosis fungoides (MF) and its leukemic variant, Sézary syndrome (SS), comprise the majority of CTCLs. Clinically, MF typically presents with isolated patches that may progress to infiltrated plaques, tumors, and diffuse erythema with involvement of lymph nodes and other visceral organs and less frequently peripheral blood; leukemic CTCL (L-CTCL)/SS meanwhile often presents de novo with diffuse erythema (erythroderma) and

This article is part of the Topical Collection on *T-Cell and Other Lymphoproliferative Malignancies*

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lymphadenopathy in addition to peripheral blood involvement [2]. Although many patients with early-stage disease have indolent disease with a normal life expectancy, advanced stages are associated with a poor prognosis [3]. Treatment of early stage disease (i.e., stage I–IIA) typically consists of skin-directed therapies (phototherapy, localized or generalized electron-beam radiation, topical agents), while systemic treatments are reserved for refractory, extensive, and/or advanced disease. Although many agents have been utilized in the treatment of MF/SS, no single regimen has been identified as superior; furthermore, duration of response is often limited, indicating a need for identifying novel agents and therapeutic targets in these patients [4]. Below, we review the recent literature regarding the pathogenesis and systemic treatments of MF/SS.

Pathogenesis of CTCL

Mycosis Fungoides and Sézary Syndrome: distinct clinical entities arising from different T memory cells

MF and its leukemic variant, SS, have traditionally been considered diseases on a single spectrum. The elucidation by Sallusto and colleagues [5] at the turn of the century of two distinct memory T cell populations provided the conceptual cornerstone that MF and SS may indeed be distinct diseases, arising from functionally and phenotypically different T cell populations. The first population, which the authors termed central memory T cells (T_{CM}), is characterized by L-selectin and CCR7 expression and is composed of lymph node-homing, circulating cells. The second population, termed effector memory T cells (T_{EM}), does not express CCR7 and are tissue-homing cells with the capacity to migrate into peripheral sites, including the skin. Several years later, Clark et al. demonstrated that the majority of T_{EM} in the skin express skin-homing addressins, including CCR4 and CLA [6]. Furthermore, while the majority of CLA-positive T memory cells were found to be resident in the skin, a minority of circulating T_{CM} cells also expressed CLA, suggesting that a subset of T_{CM} are capable of migrating to the skin. Campbell et al. subsequently demonstrated that the neoplastic cells in SS/L-CTCL patients in both the peripheral blood and skin lesions expressed a $CCR7^{+}$/L-$selectin^{+}$ T_{CM} immunophenotype, while skin lesions from patients with classic mycosis fungoides had no discernible T_{CM} present and demonstrated a T_{EM} phenotype [7]. These findings suggest that SS/L-CTCL and mycosis fungoides may be distinctly separate entities, SS/L-CTCL being a malignancy arising from T_{CM} while MF being that of T_{EM}. The same authors presented additional evidence to support this through their treatment of MF and SS/L-CTCL patients with alemtuzumab, a monoclonal anti-CD52 antibody [2]. They noted that alemtuzumab effectively targeted circulating T_{CM} cells in peripheral blood and skin but not T_{EM} cells. This correlated with patients who presented with SS responding to therapy, while those with classic MF did not. While the treatment of MF and SS has traditionally been approached together in clinical trials, these findings indicate that future treatments may better target one of these T cell subsets over the other and therefore may benefit from being explored separately.

Immunogenetic and Molecular Investigations

The pathogenesis of CTCL has long been proposed to arise from antigenic stimulation in genetically susceptible individuals, and indeed, some data suggest that MF arises in the setting of chronic inflammation [8]. Brazzelli and colleagues present evidence that suggests specific HLA alleles may be associated with a susceptibility to the development of MF, and distinct alleles may be associated with a better or worse prognosis [9, 10]. In particular, patients with HLA-DQB1*05 are associated with the poorest prognosis. Other recent studies have focused on specific molecular pathways in disease. In particular, overexpression of TOX (thymocyte selection-associated HMG-box) has been highlighted as a possible molecular marker in MF that distinguishes it from benign inflammatory skin disease [11, 12]. TOX has been found to accelerate the proliferation of malignant cells in MF in in vitro studies, suggesting that it may also play a role in pathogenesis and/or disease progression [12]. In recent years, several groups have shown that gene expression in early MF varies from that of late disease and SS. Tang et al. demonstrated that T-plastin (PLS3) gene expression is significantly upregulated by Sézary cells, which are not present in early MF [13]. Ralfkiaer and colleagues identified specific differences in expression of micro-RNAs between early MF and advanced disease [14]. These studies further support that different T cell subsets are responsible for different disease manifestations of MF and SS/L-CTCL.

Single-Agent Systemic Therapies

FDA-approved single-agent systemic therapies for CTCL include oral bexarotene, vorinostat, and intravenous (IV) romidepsin and denileukin diftitox. Interferons (IFN) alfa and gamma, gemcitabine, liposomal doxorubicin, and methotrexate are also frequently employed in these patients [15]. Below, we review recent investigations of single-agent systemic therapies for the treatment of MF/SS.

Histone Deacetylase Inhibitors

Vorinostat and Romidepsin

The histone deacetylase (HDAC) inhibitors are a class of drugs that allows chromatin to maintain an open structure, resulting in the activation of gene transcription, including those involved in apoptosis and inhibition of tumor cell growth [16]. There are several classes of histone deacetylases, including zinc-dependent enzymes (class I, II, and IV) and class III enzymes, which are zinc-independent and are not currently targeted by any of the available histone deacetylase inhibitors [17–19]. Vorinostat (Zolinza; Merck), an oral suberoylanilide hydroxamic acid derivative [20, 21], was the first drug in this class approved by the Food and Drug Administration (FDA) for the treatment of CTCL in 2006. Romidepsin (Istodax; Celgene), a selective class I HDAC inhibitor, received FDA approval in IV formulation for the treatment of refractory CTCL in 2009. In 2011, Romidepsin also received FDA approval for the treatment of refractory or relapsed peripheral T cell lymphoma (PTCL). Of note, Kim et al. found that a significant number of patients treated with romidepsin experienced a clinically meaningful reduction in pruritus, including a subset who did not achieve any objective clinical response. Thus, romidepsin may provide benefit beyond clinical response, particularly in view of the compromised quality of life MF/SS patients experience secondary to pruritus [22].

Panobinostat

Panobinostat is a potent HDAC inhibitor with activity against all class I, II, and IV HDAC enzymes [15, 23]. In a 2012 study, Duvic et al. evaluated 139 patients with stage IB-IVA MF/SS treated with panobinostat 20 mg/day, 3 days per week, in 28-day cycles until disease progression, intolerance, or discontinuation [15]. Because of the possibility that response to panobinostat may be lower in patients who previously experienced failure with oral bexarotene, patients in this study were stratified based on prior exposure to bexarotene with a total of 79 patients in the bexarotene-exposed group and 60 patients in the bexarotene-naïve group. The authors report an overall response rate (ORR) of 17.3 % for all patients (n=24), including response rate of 15.2 % in the bexarotene-exposed patients and 20.0 % in bexarotene-naïve patients. The most common side effects noted were thrombocytopenia, gastrointestinal (GI) distress, fatigue, and decreased appetite. Additional side effects included asthenia, cytopenia, dysgeusia, elevated creatinine, headache, and hypertriglyceridemia. Panobinostat is FDA approved for use in multiple myeloma but not CTCL.

Belinostat

Belinostat is a novel hydroxamate HDAC inhibitor of class I, II, and IV HDACs that has been demonstrated to have antitumor activity in a wide range of cancer cell lines [24, 25]. A study by Foss et al. published in 2014 evaluated the treatment of relapsed or refractory PTCL and CTCL with belinostat administered as 30-min IV infusion of 100 mg/m^2/day on days 1–5 of a 21-day cycle [25]. Dose escalation to 1200 mg/m^2/day for cycle 2 and to 1400 mg/m^2/day for cycle 3 was permitted based on patient tolerability. Twenty-nine patients with CTCL were included in the study, including 24 with MF/SS. In the CTCL group, the response rate was 13.8 % (n=4), including 3 complete responses (CR) and 1 partial response (PR). Side effects from drug noted in the study included GI distress, fatigue, pyrexia, dizziness, infusion site pain, pruritus, anorexia, headache, peripheral edema, rash, hypokalemia, and dyspnea.

Monoclonal Antibodies

Monoclonal antibodies with diverse targets are increasingly being utilized and investigated for many conditions, including both inflammatory diseases and malignancies. Monoclonal antibodies in the treatment of non-cutaneous hematolymphoid malignancies are covered in further depth elsewhere in this series.

Alemtuzumab (Campath-1H; Sanofi)

Alemtuzumab is a humanized IgG1 anti-CD52 monoclonal antibody FDA-approved for the treatment of B cell chronic lymphocytic leukemia (CLL) in 2007. In 2014, alemtuzumab also received FDA approval for the treatment of multiple sclerosis. Several studies have previously demonstrated short-term efficacy of alemtuzumab in advanced MF/SS, suggesting that it may be particularly useful as salvage therapy in these patients [26–30]. De Masson et al. recently published a study evaluating long-term efficacy and safety of alemtuzumab in advanced-stage CTCL patients with promising results [31]. Thirty-nine patients with stage IIB–IV CTCL (MF 16, SS 23) were treated with 30 mg IV or subcutaneous (SC) 2–3 times weekly during the induction phase, followed by 30 mg weekly in the maintenance phase with progressive intervals between treatments. The authors observed an ORR of 51 % (20/39), including 70 % in SS patients (16/23) and 25 % in MF patients (4/16). After a median follow-up period of 24 months, eight patients were still alive (CR=4, PR=4). Adverse side effects noted in the study included profound lymphopenia, infections, acute coronary syndrome, ischemic colitis, deep venous thrombosis, serum sickness-like reaction, and infusion-site reactions.

As discussed previously (see Pathogenesis), Clark and colleagues observed dramatic responses in patients with L-CTCL/SS treated with low-dose SC alemtuzumab [2]. Eighteen patients with confirmed peripheral blood involvement by CTCL were treated with alemtuzumab 10 mg SC three times weekly for a minimum of 6 weeks; all experienced improvement of peripheral blood disease, while 89 % demonstrated improvement of skin disease, including 50 % CR. This was in contrast to two patients with skin-limited MF, who demonstrated no response. These findings, along with their additional investigations, demonstrate that alemtuzumab acts on circulating T_{CM} cells and not skin-homing T_{EM} cells. Additionally, the authors noted—despite the absence of circulating B and T cells—no infections in their patients. This is in contrast to CLL patients treated with alemtuzumab, where drug administration is associated with immunosuppression and reactivation of systemic CMV [32]. The authors propose that these findings suggest that skin resident T_{EM} can function to protect the skin from infection in the absence of circulating T cells. In a recent follow-up series, the same authors report 23 patients with peripheral blood disease treated with low-dose alemtuzumab (10 mg SC, three times weekly) [33], in which all patients with diffuse erythema without plaques or tumors (n=17) demonstrated dramatic response, including 13/17 CR. Meanwhile, none of the six patients with discrete plaques or tumors (with or without background erythema) experienced remission. These findings support that circulating T_{CM} cells can cause clinical erythroderma through migration to the skin and that clinical evaluation may help determine who will respond to low-dose alemtuzumab.

Brentuximab Vedotin (Adcetris; Seattle Genetics)

Brentuximab vedotin is an anti-CD30 monoclonal antibody that received expedited FDA approval for the treatment of refractory Hodgkin's lymphoma and systemic anaplastic large cell lymphoma (ALCL), a subtype of peripheral T cell lymphoma. CD30 expression in MF often accompanies large cell transformation and, overall, is associated with more aggressive clinical course and reduced survival [34]. While multiple large studies evaluating brentuximab in the treatment of CTCL are ongoing [35], several small studies/case series have demonstrated promising results [36–39]. Duvic et al. reported 28 MF patients treated with brentuximab in whom an ORR of 50 % (n=14) was seen. Of interest, not all patients who responded were characterized by CD30-positive disease [38].

Mogamulizumab (KW-0761)

Mogamulizumab is a defucosylated, humanized anti-CCR4 monoclonal antibody that, due to removal of fucose, elicits a more potent antibody-dependent cellular cytotoxicity (ADCC) than conventionally produced antibodies [40, 41]. CCR4 (CC chemokine receptor 4) is the receptor for macrophage-derived chemokine and thymus- and activation-regulated chemokine (TARC), which is presented on T helper type 2 (Th2) lymphocytes as well as other regulatory T cells [42, 43]. CCR4-expressing neoplastic T cells have been demonstrated in approximately 40 % of patients with CTCL [44]. It has been proposed that interactions between CCR4 and its ligands may play a role in malignant T cell trafficking and distant metastasis [45]. A phase II study of mogamulizumab 1 mg/kg weekly for 8 weeks in Japanese patients with relapsed CCR4-positive PTCL (n=29) and CTCL (n=8) demonstrated an ORR of 35 % [46]. Duvic et al. reported earlier this year results of a phase I/II study of 38 patients with stage IB or greater MF/SS who received mogamulizumab IV starting at 0.1 mg/kg weekly with dose escalation for four weeks of a 6-week cycle (phase 1), followed by 1 mg/kg every 2 weeks until disease progression [47]. The authors note an ORR of 36.8 %, with a higher rate of response in SS patients (47.1 %) compared to that in MF patients (28.6 %). Mogamulizumab was generally well-tolerated, with side effects of nausea, chills, infusion reactions, headache, pyrexia, fatigue, diarrhea, pruritus, and cutaneous drug eruptions. A phase III trial comparing mogamulizumab to vorinostat therapy in CTCL patients is currently under way [48].

Traditional/Cytotoxic Chemotherapeutic Agents

Traditional cytotoxic chemotherapeutic agents are generally employed in CTCL only in advanced, refractory disease after biological therapy has been exhausted, due to the high risks of myelosuppression in these patients with underlying immunocompromise [49, 50]. Among these, few have been well-studied in CTCL, but include pentostatin, gemcitabine, chlorambucil, and doxorubicin. Below, we highlight recent findings of several agents from this class.

Pralatrexate (Folotyn; Allos Pharmaceuticals)

Pralatrexate (PDX) is a synthetic folate analog antimetabolite that competitively inhibits dihydrofolate reductase (DHFR). PDX enters cells through the reduced folate carrier type-1 protein, which has been shown to be overexpressed on cancer cells compared to normal cells [51, 52]. Once present intracellularly, PDX competitively inhibits polyglutamylation by the enzyme folate-polyglutamyl synthetase, resulting in a depletion of thymidine and other biologic molecules, with subsequent interference with DNA synthesis and cell death [53]. Multiple in vitro and in vivo assays have found PDX to be 5- to 40-fold more cytotoxic than methotrexate (MTX) [52, 54].

Results of the PROPEL (pralatrexate in patients with relapsed or refractory peripheral T cell lymphoma) study [55] led to accelerated FDA approval for pralatrexate in the

treatment of relapsed or refractory of PTCL in 2009. The study included 12 patients with transformed MF who received a median of 10 doses of drug, starting at 30 mg/m^2/week for 6 weeks in a 7-week cycle. In a subgroup efficacy analysis of these patients, Foss et al. observed an ORR of 25 % (n=3) by independent central review and 58 % (n=7) by investigator assessment [56]. The discrepancy was attributed to challenges that accompany photodocumentation of cutaneous lesions. These initial results led to larger studies of PDX in patients with CTCL. In a dose-finding study, Horwitz et al. treated 54 patients with stage IB or greater CTCL (38 MF, 15 SS, and 1 ALCL) with a starting dose of 30 mg/m^2/week by IV push for 3 consecutive weeks of a 4-week cycle [57]. The ORR across all patients was 41 % (n=22), including 3 CR and 19 PR. The authors further established an ideal starting dose of 15 mg/m^2/week for 3 weeks of a 4-week cycle in CTCL patients, which was significantly lower than doses established for the treatment of PTCL. Pralatrexate demonstrated high activity with acceptable toxicity in CTCL patients with this regimen. The authors also noted a 46 % response rate in patients who had progressed following MTX therapy, suggesting that PDX may exhibit potentially non-cross-resistant mechanism of action compared to MTX. A second study by Talpur et al. evaluated 26 patients with stage IB or greater MF. [58] Twelve patients received PDX as a single agent with initial doses of 10, 15, 20, or 30 mg/m^2 weekly (3 patients each) by IV push for 3 weeks of a 4-week cycle. Fourteen patients received PDX 15 mg/m^2 combined with oral bexarotene 150–300 mg/m^2 daily. The ORR for all patients was 42 % (11/26), including 33 % (4/12) in the PDX-only group and 50 % (7/14) in the combination group. While these initial results suggest that combination therapy with bexarotene may be superior to PDX monotherapy in the treatment of CTCL, the number of patients is small and thus larger-scale studies are needed to further assess this possibility.

Side effects of PDX include most commonly stomatitis and fatigue, as well as nausea, edema, anemia, pyrexia, lymphopenia, thrombocytopenia, and skin toxicity [57]. Leucovorin rescue may minimize PDX dose-limiting stomatitis without compromising drug efficacy [59].

Pegylated Liposomal Doxorubicin (Doxil, Caelyx; Janssen)

Doxorubicin is currently the most used anthracycline for advanced CTCL. It is employed in the treatment of NHL as part of the CHOP regimen and is FDA-approved for the treatment of HIV-related Kaposi sarcoma. While doxorubicin in the treatment of MF was first reported by Levi in 1977 [60], several recent studies have confirmed its role in MF/SS.

In an EORTC-initiated phase II trial for pegylated liposomal doxorubicin, Dummer et al. studied a cohort of 49 patients with stage IIA–IVB MF from 9 centers in 6 countries [61]. The patients were treated with 20 mg/m^2 IV on days 1 and 15 every 28 days (1 cycle) for up to 6 cycles. The ORR was 40.8 %, including 3 patients with CR and 17 patients with PR. In 2013, Straus et al. published results of a phase II trial using doxorubicin HCl liposome injection in 37 patients with stage IB–IV disease, including 10 patients with SS [62]. Subjects were treated with 20 mg/m^2 IV every 2 weeks for 16 weeks. All patients who did not progress also received bexarotene 300 mg/m^2 daily starting at week 16 for an additional 16 weeks. Forty-one percent responded with a CR observed in 2 patients (both stage IV) and a PR in 12 patients. The median overall survival duration was 18 months; it was noted that there were 22 deaths following discontinuation of protocol treatment. Side effects of doxorubicin include cardiotoxicity, dose-dependent cytopenia, GI symptoms, palmoplantar erythrodysesthesia, and alopecia.

Bendamustine (Treanda; Cephalon)

Bendamustine, an IV nitrogen mustard alkylating agent, was approved by the FDA in 2008 for the treatment of indolent B cell NHL and CLL. Although its evaluation in CTCL is limited, several studies have suggested benefit in MF/SS. In a study of 60 patients with refractory/relapsed T cell lymphoma

Table 1 Novel combination chemotherapy regimens in MF/SS

Agents	Response rate (responders/total)	Dosing	Study
Pentostatin, cyclophosphamide, and bexarotene	5/5 MF; 2/3 SS	4 mg/m^2 q 2 weeks; 600 mg/m^2 q 2 weeks; 300 mg/m^2 qd respectively ×8 months	Calderon Cabrera C et al. [84]
Doxorubicin±bexarotene	14/34 (doxorubicin only); 7/15 (doxorubicin+bexarotene)	Liposomal doxorubicin 20 mg/m^2 q 2 weeks; b exarotene 300 mg/m^2/day	Straus DJ et al. [62]
Gemcitabine+bexarotene	11/35 at 12 weeks; 5/35 at 24 weeks (results lower than those previously reported for gemcitabine single-agent therapy)	Gemcitabine 1000 mg/m^2 IV days 1 and 8×4 cycles; bexarotene 300 mg/m^2/day	Illidge T et al. [85]
Vorinostat+bexarotene	4/23	Vorinostat 200 mg/day; bexarotene 300 mg/m^2/day	Dummer et al. [86]

that included two MF patients, bendamustine 120 mg/m^2/day over 30–60 min was administered on days 1 and 2 every 3 weeks, for a total of six cycles [63]. An ORR of 50 % was noted; however, the MF patients were not analyzed as a subgroup. In a second trial that enrolled three patients with advanced stage MF/SS, two patients experienced PR at doses of 60-100 mg/m^2 [64]. Side effects of bendamustine include GI symptoms, myelosuppression, cytopenia, infusion site reactions, skin reactions, and infections. The latter includes CMV reactivation [65].

Other Systemic Agents

Forodesine (BCX-1777, Immucillin H; BioCryst)

Forodesine is a purine nucleoside phosphorylase (PNP) inhibitor, the action of which results in the accumulation of deoxyguanosine triphosphate (deoxyGTP), which in turn inhibits DNA synthesis with resultant suppression of cell proliferation [66, 67]. Selective T cell depletion occurs with PNP inhibition due to relatively high level of kinase and low level of nucleotidase activity compared to those in other cells [68–70]. Forodesine is available in both an oral and IV formulation and has been granted orphan drug status by the FDA.

In a phase II study published in 2013 by Dummer and Duvic et al., 101 patients with stage IIB or greater MF/SS administered 200 mg orally daily (roughly equivalent to 80 mg/m^2) were assessed for drug efficacy with an ORR of 11 % [71]. The lower response rate compared to prior smaller-scale studies was proposed to be due to the lower dose of medication given in this study compared to prior studies, which demonstrated ORR >50 % [72, 73]. Forodesine is generally well-tolerated, with side effects including nausea, fatigue, reversible lymphopenia, and cutaneous infections [71, 72].

Multi-agent Systemic Chemotherapies

As mentioned previously, biologic therapy is favored over traditional cytotoxic chemotherapy agents for initial therapy in most cases of CTCL due to risks associated with immunosuppression with the latter. Traditional multi-agent chemotherapy regimens, however, along with clinical trials, are first-line therapy for aggressive/rapidly progressive CTCL, including transformed MF [74]. While no large controlled studies evaluating these regimens in MF/SS exist, these include CHOP, EPOCH, hyper-CVAD, and others [75–83]. Overall, however, the efficacy of multi-agent chemotherapy in the treatment of MF/SS is not well-established. A recent retrospective study by Hughes and colleagues suggests, however, that chemotherapeutic agents, either as single-agent or multi-agent treatment, are no more effective—and in fact may be inferior—compared to biological agents such as IFN and HDAC inhibitors [4]. This study is the first in the literature to attempt to directly compare the efficacy of conventional chemotherapy with biological agents in CTCL. Using time to next treatment as the primary endpoint and a surrogate for efficacy, the authors also noted that traditional chemotherapy may be most effective when it is used as initial therapy, although in practice it is often employed after multiple failed treatments. More recently, multiple studies have evaluated novel multi-agent combinations, including combinations of different biological agents as well as biological agents with traditional chemotherapeutics, with varied results (Table 1).

Conclusion

Although many patients with early CTCL have indolent disease with a normal life expectancy, advanced stages are associated with a poor prognosis. Since the duration of response to systemic therapies is often limited, there continues to be a need for novel agents and therapeutic targets in these patients. As the pathogenesis of MF/SS becomes further elucidated, identification of specific molecular targets against different T cell subsets may result in more effective therapies in this complex disease.

Compliance with Ethical Standards

Conflict of Interest Catherine G. Chung and Brian Poligone each declare no potential conflicts of interest.

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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