Management of cutaneous T cell lymphoma: new and emerging targets and treatment options

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Abstract: Cutaneous T cell lymphomas (CTCL) clinically and biologically represent a heterogeneous group of non-Hodgkin lymphomas, with mycosis fungoides and Sézary syndrome being the most common subtypes. Over the last decade, new immunological and molecular pathways have been identified that not only influence CTCL phenotype and growth, but also provide targets for therapies and prognostication. This review will focus on recent advances in the development of therapeutic agents, including bortezomib, the histone deacetylase inhibitors (vorinostat and romidepsin), and pralatrexate in CTCL.

Keywords: novel targets, histone deacetylase inhibitors, pralatrexate, bortezomib, cutaneous T cell lymphoma

Introduction
Cutaneous T cell lymphomas (CTCL) represent a heterogeneous group of non-Hodgkin lymphomas characterized by an initial infiltration of the skin with clonally-derived malignant T lymphocytes of the CD4\(^+\) CD45RO\(^+\) phenotype that generally lack normal T cell markers, such as CD7 and CD26.\(^1\) The diversity of clinical and pathologic manifestations among subsets of CTCL has led to much controversy over its diagnosis and classification and to the establishment of consensus guidelines by a joint effort of the World Health Organization and European Organization for Research and Treatment of Cancer (WHO-EORTC) in 2005.\(^2\)

The two most common types of CTCL are mycosis fungoides (50%–72%), which is generally indolent in behavior, and Sézary syndrome (1%–3%), an aggressive leukemic form of the disease (Table 1).\(^2\)\(^5\) Other types include primary cutaneous CD30\(^+\) lymphoproliferative disorders, subcutaneous panniculitis-like T cell lymphoma, and the group of primary cutaneous peripheral T cell lymphomas that includes the provisional entities of cutaneous aggressive epidermotropic CD8\(^+\) T cell lymphoma, cutaneous γδT cell lymphoma, and cutaneous CD4\(^+\) small/medium-sized pleomorphic T cell lymphoma.\(^4\)\(^6\)

Mycosis fungoides and Sézary syndrome together comprise 54% of all CTCL.\(^2\) The annual incidence of CTCL in the United States has increased from 2.8 per million (1973–1977) to 9.6 per million (1998–2002) according to data from Criscione and Weinstock.\(^5\)

Median age at presentation is between 50 and 70 years,\(^5\)\(^7\)\(^8\) although pediatric and young adult cases do occur.\(^9\)\(^10\) Mycosis fungoides classically presents with an indolent course and slow progression over years or sometimes decades. The disease may evolve from patches to infiltrated plaques and eventually to tumors (Figure 1A and B). However, about 30% of
Table 1 European Organization for Research and Treatment of Cancer consensus classification for primary cutaneous lymphomas with relative frequency and 5-year survival

<table>
<thead>
<tr>
<th>WHO-EORTC</th>
<th>Frequency (%)</th>
<th>5-year survival (%)</th>
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<tr>
<td>Cutaneous T cell and natural killer cell lymphoma Indolent</td>
<td></td>
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<tr>
<td>Mycosis fungoides</td>
<td>44</td>
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<td>80</td>
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<tr>
<td>• Pagetoid reticulosis</td>
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<td>• Granulomatous slack skin</td>
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<td>100</td>
</tr>
<tr>
<td>CD30+ lymphoproliferative disorders</td>
<td></td>
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<tr>
<td>• Anaplastic large cell lymphoma</td>
<td>8</td>
<td>95</td>
</tr>
<tr>
<td>• Lymphomatoid papulosis</td>
<td>12</td>
<td>100</td>
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<tr>
<td>Subcutaneous panniculitis-like T cell lymphoma</td>
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<td>CD4+ small/medium pleomorphic T cell lymphoma</td>
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<tr>
<td>Aggressive</td>
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</tr>
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<td>Sézary syndrome</td>
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<tr>
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<td>• Cutaneous γδ T cell lymphoma</td>
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<td>Marginal zone lymphoma</td>
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<td>Large B cell lymphoma of the leg</td>
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<tr>
<td>Intravascular large B cell lymphoma</td>
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Abbreviations: WHO, World Health Organization; EORTC, European Organization for Research and Treatment of Cancer.

patients present with skin tumors (T3) or erythroderma (T4) at initial presentation.8 Sézary syndrome is a much more aggressive disease. Patients with Sézary syndrome present with erythroderma, circulating malignant T cells (Sézary cells), and severe disabling pruritus with or without associated lymphadenopathy (Figure 2). The TNMB (tumor, node, metastasis, blood) classification for clinical staging is used according to the Mycosis Fungoides Cooperative Group staging system,11 established in 1979 by Bunn and Lamberg, which was revised by the International Society for Cutaneous Lymphomas/European Organization for Research and Treatment of Cancer (EORTC) staging proposal in 2007.12 Advanced clinical stages range from IIB (skin tumors) to IVB (visceral disease).

While the overall survival rate of patients with mycosis fungoides is 68% at 5 years and 17% at 30 years, the specific survival of patients ranges widely, depending on
T classification and stage at initial presentation. The largest study, consisting of 525 patients, showed an overall survival of 97% in patients with T1 (less than 10% body surface involvement) at 5 years, compared with 40% and 41% in T3 and T4 disease, respectively. Other studies have shown that elevated lactate dehydrogenase, large-cell transformation, and folliculotropic mycosis fungoides are associated with a worse prognosis. Patients with Sézary syndrome have an estimated 5-year survival of 24%. Recent analyses of outcomes in patients with mycosis fungoides or Sézary syndrome using the International Society for Cutaneous Lymphoma/EORTC revised staging proposal established that the presence of a T cell clone in blood (identical to the cutaneous T cell clone) in the absence of morphologic evidence of blood involvement (B0b) was also associated with a significantly worse overall survival and disease-specific survival compared with those patients with no peripheral blood T cell clone (B0a).

Research on new therapies for CTCL is largely centered on defining novel targets for therapy. The International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the EORTC have developed consensus guidelines to facilitate collaboration in clinical trials. These proposed guidelines consist of: recommendations for standardizing general protocol design; a scoring system for assessing tumor burden in skin, lymph nodes, blood, and viscera; definition of response in skin, nodes, blood, and viscera; a composite global response score; and a definition of end points. Although these guidelines were generated by consensus panels, they have not been prospectively or retrospectively validated by analysis of large patient cohorts. This review focuses on current and new discoveries that have provided targets for therapy in patients with mycosis fungoides or Sézary syndrome. We will briefly give an overview of recent molecular discoveries and dysregulated signaling pathways, followed by a presentation of current and novel topical, biological, and chemotherapeutic treatments for CTCL patients.

Immunologic and molecular findings in mycosis fungoides and Sézary syndrome

Immunologic mechanisms of pathogenesis

Most malignant T cells in CTCL are clonally derived from CD4+ T helper memory cells. In the early stages of mycosis fungoides, the T cell infiltrate consists of both malignant CD4+ and reactive CD8+ T cells, with a dominance of Th1 cytokines, such as interferon-gamma (IFN)-γ, interleukin (IL)-12, and IL-2. In the later stages, there is a gradual increase in malignant CD4+ cells, a decrease in nonmalignant CD8+ cells, and a shift to Th2 cytokine dominance (IL-4, IL-5, IL-10, and IL-13). These changes correlate with disease progression, host immunosuppression, and susceptibility to infection. Biologic immune modifiers, such as IFN-α, IFN-γ, and IL-12, are therapeutically effective in CTCL by stimulating Th1 cytokines and boosting host immune responses. The recently discovered Th17 lineage of CD4+ T cells functions in host protection against extracellular bacteria and fungi. Th17-derived cytokines (IL-17, IL-21, and IL-22) have been implicated in autoimmunity. Recently, the Th1/Th2 paradigm of CTCL has been revisited, including a role for a Th17-producing T cell (Th17) population in cutaneous lesions of patients with mycosis fungoides or Sézary syndrome. Interestingly, IL-17 was not measurable in serum samples of patients with mycosis fungoides or Sézary syndrome, suggesting that this cytokine may only play a role in cutaneous lesions. In another study, IL-17 protein was found to be mediated by IL-2/IL-15 through the Jak3/STAT3 pathway. Other immune regulatory molecules found to be overexpressed in CTCL include IL-15, IL-16, and IL-21, and programmed death-1 (PD-1).

Controversial results have been found for PD-1 expression. Increased PD-1 expression has been shown on circulating CD4+ cells in patients with Sézary syndrome...
when compared with patients with mycosis fungoides, which could imply a role for an increase in PD-1 expression in the progression of tumors.\textsuperscript{26} However, recent data showed increased PD-1 in pseudolymphoma and cutaneous CD4+ small/medium-sized pleomorphic T cell lymphoma.\textsuperscript{28} Further research is needed in this area to determine whether the increase in PD-1 expression protects tumor cells from elimination, or if the increased PD-1 expression is a response of immunocompetent cells that are simply chronically stimulated by tumor antigens.

Chemokines and chemokine receptors in CTCL have been reviewed by others.\textsuperscript{29,30} They mediate not only trafficking of malignant T cells into the skin, but also their survival, possibly due to activation of prosurvival pathways. Chemokine receptor 4 (CCR4) is not only necessary for skin-homing of normal CD4+ T lymphocytes, but also for malignant CTCL cells.\textsuperscript{31,32} Both CCR4 and CCR10 have been shown to be highly expressed in CTCL skin lesions\textsuperscript{33} and in the peripheral blood cells of patients with mycosis fungoides or Sézary syndrome.\textsuperscript{34,35} While CCL17, a CCR4 ligand expressed on epidermal keratinocytes, has been implicated in both skin and nodal homing of CTCL cells, CCL27, a CCR10 ligand expressed on keratinocytes, endothelial cells, and dendritic cells, facilitates extravasation and migration of CTCL cells into the skin and epidermis. CCL27, a CCR10 ligand expressed on keratinocytes, has been implicated in both skin and nodal homing of CTCL cells. Anti-CCR4 is currently being evaluated in clinical trials including CTCL patients.

Naturally occurring regulatory T cells (Tregs, CD4+ CD25+ FOXP3+ phenotype) suppress the activity of other immune cells and thus maintain immunological tolerance. Tregs appear to be dysregulated in CTCL.\textsuperscript{36} Early cutaneous lesions in patients with mycosis fungoides contain numerous FOXP3+-infiltrating Tregs that decrease in number in advanced lesions. The high frequency of FOXP3+-infiltrating Tregs may suppress tumor proliferation and have been correlated with improved survival.\textsuperscript{36} Patients with Sézary syndrome have very low levels of Tregs but high levels of malignant T cells expressing a Treg phenotype (FOXP3+ CD25–). These malignant FOXP3+ Tregs express CTLA-4, IL-10, and transforming growth factor-\(\beta\), which suppress immunity and diminish the antitumor response.\textsuperscript{37}

Cytotoxic T lymphocyte antigen (CTLA-4) is a coinhibitory molecule expressed on T cells that inhibits T cell activation and proliferation\textsuperscript{37} and confers resistance against activation-induced cell death.\textsuperscript{39} Tregs also constitutively express CTLA-4, which is necessary for their functioning to maintain peripheral tolerance and to prevent autoimmunity.\textsuperscript{39,40} High CTLA-4 expression was found in peripheral blood mononuclear cells from patients with mycosis fungoides, and higher expression levels correlated with increased tumor burden. Th1-derived cytokines, such as IL-2 and IFN-\(\gamma\), upregulate expression of CTLA-4.\textsuperscript{41} Whether increased CTLA-4 expression relates to Treg-like properties that CTCL cells acquire during disease progression is not clear; further research is needed to prove this concept. Anti-CTLA-4 (ipilimumab) is an important immunotherapeutic strategy in melanoma; the association of dysregulated CTLA-4 in CTCL suggests a potential therapeutic target in this disease.

Epigenetic mechanisms of pathogenesis

DNA methylation of CpG islands in promoter regions is an epigenetic mechanism of gene expression that tightens chromatin around nucleosomes and interferes with binding of transcription factors.\textsuperscript{42} This has been shown to downregulate expression of tumor suppressor genes, leading to carcinogenesis in several tumor types.\textsuperscript{43} In CTCL, promoter hypermethylation leads to dysregulation of the cell cycle (\(p15/p16/p73\)), apoptosis (\(TMS1/p73\)), DNA repair (\(MGMT\)), chromosomal instability (\(CHFR\)), and microsatellite instability (\(MLH1\)) genes and proteins.\textsuperscript{44–48} Promoter hypermethylation of \(p15/p16\), and \(MLH1\) was found in both early and advanced stages of mycosis fungoides and Sézary syndrome, suggesting that early epigenetic alterations were responsible for the inactivation of these genes.\textsuperscript{46–48}

When genes are hypermethylated and silenced, the histones are in a deacetylated state.\textsuperscript{42} Acetylation of histones in nucleosomes alters conformation of chromatin. Histone deacetylases (HDACs) remove acetyl groups, leading to compaction of chromatin and repression of transcription.\textsuperscript{49} In addition to their action on histones, HDACs also regulate various transcription factors, such as the p53 tumor suppressor and E2F oncogene.\textsuperscript{49} HDACs were initially developed to restore tumor suppressor and cell regulatory genes by inducing histone hyperacetylation.\textsuperscript{50}

Apoptotic mechanisms of pathogenesis

Defective regulation of apoptosis is a central feature of the pathology of several lymphoma types, including mycosis fungoides and Sézary syndrome. Apoptosis can be triggered by death receptors that belong to the tumor necrosis factor receptor family or by aberrations in expression of the B cell lymphoma-2 (Bcl-2) family. Malignant CD4+ T cells from cutaneous lesions and peripheral blood samples in mycosis fungoides and Sézary syndrome have decreased and/or defective Fas expression, and decreased Fas expression has been correlated with more aggressive disease as well as resistance
to Fas-mediated apoptosis.51–54 Thus, downregulation of Fas may be one way in which CTCL cells become resistant to chemotherapy. Downregulation of Fas in CTCL occurs through multiple mechanisms, ie, mutations in the Fas gene,52 production of nonfunctioning splice variants,59 and promoter hypermethylation.56 In this context, malignant T cells in CTCL may acquire resistance to FasL signaling through increased expression of cFLIP, an intracellular apoptosis inhibitor.51

The expression of other antiapoptotic molecules, such as p53 and Bcl-2 family members, has been studied in CTCL. In one in vitro study, p53 mutations were identified in tumor stage mycosis fungoides, but not in patch/plaque mycosis fungoides.57 In another study, there was no correlation between clinical stage and p53 mutations.58 One pathway being targeted for antineoplastic therapy is the antiapoptotic Bcl-2 and Bcl-2-like family of proteins. T cells generally express Bcl-2 that inhibits apoptosis and is widely and stably expressed in all stages of mycosis fungoides.59 Data suggested that inhibition of Stat3 signaling in CTCL cells through the Jak kinase inhibitor, Ag490, induced apoptosis through decreased expression of antiapoptotic Bcl-2 and increased expression of the proapoptotic Bax protein.60 Surprisingly, other investigators found late-stage disease and shorter survival time were correlated with decreased Bcl-2 expression.59 However, information about quantification of Bcl-2 protein expression was not provided. It also remains unclear whether the low expression is related to alterations of genes, such as p53, that impact Bcl-2 expression.

Polo-like kinase 1 (Plk1) is a member of the PLK family of serine/threonine kinases crucial to the cell division cycle, which has been postulated to induce oncogenesis in multiple solid and hematologic malignancies.61–64 Increased expression has been found with progression and metastasis. Plk1 expression is elevated in CTCL, and in particular is found in tumor-stage and in folliculotropic and erythroidermytic types of CTCL.65,66 In vitro studies with both small molecule inhibition and shRNA-mediated knockdown of Plk1 resulted in decreased cell growth, decreased cell viability, G2/M arrest, and apoptosis in CTCL cells.66 In addition, CTCL cell lines with p5335 and k-ras36 mutations appear to be sensitive to Plk inhibition and may serve as biomarkers for patient selection. Currently there are a number of Plk inhibitors in preclinical development,67 and results have been reported from Phase I studies for four of them (BI 2536,68 GSK 461364,69 ON-01910,70 and HMN-21471). Although these inhibitors were studied mainly in solid tumors, with modest responses reported and prolongation of stable disease at best, they have yet to be studied in CTCL. Plk1 could serve as a potential target in advanced stages, when its expression is generally high.

The existence of multiple mechanisms of oncogenesis in CTCL and the variety of mechanistic combinations in individual patients may perhaps require more individualized therapy. A recent report of cotreatment with the HDAC inhibitor, panobinostat, and the Bcl-2 antagonist, ABT-737, found synergistic induction of apoptosis in CTCL cells.72

Molecular mechanisms of pathogenesis

Genome-wide analysis of chromosomal alterations is increasingly used as a research tool in the search for novel agents to treat CTCL.73–77 Improvements in microarray technology and computational analysis of genomic data have led to discoveries of underlying chromosomal mutations in tumor suppressor and oncogenes involved in CTCL.73–75 Chromosomal regions with significant gains include 8q (including the MYC oncogene), 17q, and 10p13 (including GATA3, a transcription factor which promotes Th2 cytokine production).74 Additionally, a recent study suggested that amplifications on 4q12 (including KIT), 7p11.2 (including EGFR), and 17q25.1 may be highly associated with patients refractory to treatment.74 Specific oncogenes have been examined for defining new prognostic factors in CTCL. Deletions have been found on chromosomes 17p (including TP53), 10p, and 10q (including PTEN and E4S), 13q including RB1, and 9p21.3 (including CDKN2A).74

MicroRNAs (miRNAs) are small noncoding RNAs that regulate gene expression. miRNAs have been shown to become dysregulated in cancer, providing the basis for development of miRNA-targeted cancer therapies.76 A microarray screen found that five miRNAs (miR-203, miR-205, miR-326, miR-663b, and miR-711) distinguish CTCL from benign skin diseases, with an accuracy of greater than 90%.77 In tumor-stage mycosis fungoides, miR-93, miR-92A, and miR-155 were upregulated in comparison with benign inflammatory skin diseases.78 In Sézary syndrome, most miRNAs were downregulated, but miR-21, miR-486, and miR-214 were upregulated and are involved in apoptotic resistance.79 miR-21 has been shown to mediate oncogenic signaling by STAT3 and may be a possible therapeutic target for Sézary syndrome.27,80

Current and emerging therapies for early-stage disease

Patients with early-stage mycosis fungoides often present with disease limited to the skin without systemic
involvement; in these patients, a durable response can be achieved in approximately 60%–80% of cases with skin-directed therapies. Patients with early-stage disease may be effectively treated with topical agents, because previous data have demonstrated that there is no benefit to aggressive use of systemic chemotherapy.81 Existing therapeutic approaches include phototherapy with psoralen plus ultraviolet A (PUVA), narrowband ultraviolet B (NB-UVB), total electron beam irradiation (TSEBT), and topical formulations of corticosteroids, nitrogen mustard, and retinoids/retinoids. Success rates with PUVA are 90% for stage IA, 76% for stage IB, 78% for stage IIA, 59% for stage IIB%, and 61% for stage III CTCL.82–84 The most common reported acute side effects were erythema, pruritus, and nausea. Long-term exposure was associated with an increased risk for developing chronic photodamage and nonmelanoma skin cancer.84

Recent consensus from the EORTC indicates that patients with patches and thin plaques should be given NB-UVB treatment, whereas PUVA should be reserved for patients with folliculotropism mycosis fungoides, failure of NB-UVB treatment, or dark complexion, due to carcinogenic effects, as well as a paucity of available treatment centers.85 Early-stage refractory patients may benefit from combination therapies, such as NB-UVB or PUVA with low-dose systemic oral bexarotene, acitretin, or IFN-α.86 High-potency topical corticosteroids have also been shown to have an overall response rate of >90% in patch-stage mycosis fungoides, with some side effects of irritant dermatitis and cutaneous atrophy.87,88 Topical nitrogen mustard has a complete response rate of 76%–80% for stage IA and 35%–68% complete response rate for stage IB disease.89 Common side effects are contact hypersensitivity reactions. Bexarotene gel is a retinoid X receptor agonist and is approved for early-stage mycosis fungoides.90 In clinical trials, it has been shown to have an overall response rate (ORR) of 54% and a complete response rate of 10% in patients with stages IA–IIA mycosis fungoides. It commonly causes skin irritation. Tazarotene gel, a retinoic acid receptor agonist, is another topical retinoid insufficient penetration of 5-ALA and/or light.104,105 Common adverse effects of ALA include pain that occurs during light exposure, erythema, edema, and postinflammatory pigment changes.106 Due to the limited efficacy and side effect profile of ALA, other photosensitizers have been recently tested in CTCL. Methyl aminolevulinate hydrochloride, the methyl ester derivative of ALA, with greater lipophilia resulting in increased penetration and less pain, induced a complete response in six of seven cases of resistant unilaterial patch-stage mycosis fungoides, with no recurrence during follow-up periods from 12 to 34 months.107–109 Silicon phthalocyanine Pc 4 has been shown to induce apoptosis in
Peripheral blood mononuclear cells from patients with Sézary syndrome,\textsuperscript{110} Hypericin ointment, another photosensitizer, induced a response in a Phase II trial of 12 patients, with adverse effects of burning, itching, erythema, and pruritus at the site of application.\textsuperscript{111}

**Current and emerging therapies for advanced-stage disease**

**Biological therapies**

Patients with advanced disease (stage IIB–IVB) may have disseminated disease into lymph nodes and other organs, and may exhibit multiple immune derangements necessitating systemic therapy. While no regimen has been proven to prolong survival in the advanced stages, immunomodulatory regimens should be used initially to reduce the need for cytotoxic therapies. Decreased cell-mediated immunity with a dominant Th2 cytokine profile is observed in advanced stages of mycosis fungoides and Sézary syndrome. Bexarotene, immunomodulatory cytokines such as IFN-\(\alpha\), IFN-\(\gamma\), and IL-12, and extracorporeal photopheresis enhance the host antitumor response by either maintaining Th1 skewing or inhibition of Th2 cytokine production.

Extracorporeal photopheresis, approved in 1988 by the US Food and Drug Administration (FDA) for the palliative treatment of patients with CTCL, is best suited to patients with Sézary syndrome, within 2 years of disease onset, near normal counts of CD8\(^+\) T cells and natural killer cells, and modest tumor burden.\textsuperscript{112} Overall response rates have ranged from 31% to 73% when CTCL patients are treated with extracorporeal photopheresis as monotherapy, but have been shown to have greater efficacy in various combinations with IFN-\(\alpha\), IFN-\(\gamma\), granulocyte-macrophage colony-stimulating factor, and bexarotene, due to enhancement of antitumor immunity.\textsuperscript{113,114} The novel continuous flow separation system (Therakos\textsuperscript{TM} Cellex\textsuperscript{TM}) has been developed based on the current Uvar\textsuperscript{®} XTS\textsuperscript{TM} photopheresis device and is designed to reduce treatment times and extracorporeal volumes.

IFN-\(\alpha\) is one of the most widely used first-line treatments and probably the most effective single agent in the treatment of CTCL. It has shown a wide range of biologic effects, including antiviral, antiproliferative, and immunomodulatory actions. The exact mechanism by which interferons exert their antitumor effects remains unknown. Th1 cytokines support cytotoxic T cell-mediated immunity and it has been speculated that IFN-\(\alpha\) maintains or enhances a Th1 cell population balance for an effective cell-mediated response to malignant T lymphocytes. A response rate of 73% in stage IA–IIA and 60% response in stage IIB–IVA disease has been seen with IFN-\(\alpha\) monotherapy.\textsuperscript{115} When IFN-\(\alpha\) is used in combination with PUVA, both overall response rates and response duration show improvement, with studies demonstrating overall response and complete response rates of 98% and 84%.\textsuperscript{116,117} While the optimal dose and duration has not been established yet in CTCL, current experience suggests that therapy should be given at a starting dose of 1–3 million units five times weekly, with gradual escalation to 6–9 million units daily or as tolerated.

**Denileukin diftitox**

Denileukin diftitox (Ontak\textsuperscript{®}) is an IL-2 diphtheria toxin fusion protein targeted against malignant T cells expressing CD25, the high-affinity IL-2 receptor. Denileukin diftitox was approved by the FDA in 1999 for the treatment of patients with CTCL refractory to standard treatment options. In general, response rates in patients with relapsed and refractory mycosis fungoides or Sézary syndrome range from 30% to 37%.\textsuperscript{118} A recent randomized Phase III trial in CD25 + CTCL demonstrated an ORR of 44% for patients treated with denileukin diftitox versus 15.9% for patients on placebo. CTCL patients were randomly assigned to denileukin diftitox 9 \(\mu\)g/kg/day (n = 45), denileukin diftitox 18 \(\mu\)g/kg/day (n = 55), or placebo infusions (n = 44). In addition, patients treated with both doses of denileukin diftitox had a significantly longer progression-free survival than patients on placebo.\textsuperscript{119} The incidence of grade 3 and 4 capillary leak syndrome was seen in 2–3 patients (3.6%) at doses of 18 \(\mu\)g/kg/day. A key remaining question of whether response to denileukin diftitox depends on expression of CD25 was explored in a retrospective study of complete responders in previous Phase II and Phase III trials. This study found no difference in response between patients with CD25-positive and CD25-negative disease.\textsuperscript{120}

**Histone deacetylase inhibitors**

HDAC inhibitors were initially developed to modulate chromatin condensation by acetylation of histones affecting gene expression. More recently, their effects on post-translational modification of many intracellular proteins have been recognized.\textsuperscript{121} Vorinostat (suberoylanilide hydroxamic acid; Zolinza\textsuperscript{®}), an orally administrated HADC inhibitor, was approved by the FDA in 2006 for the treatment of relapsed/refractory CTCL. A Phase IIB trial was conducted in 74 patients with stage IB–IVA CTCL, including 82% with \(\geq\)stage IIB disease. ORR was 29.7%. Oral vorinostat was administered at 400 mg daily. The median time to
response was 2 months and median duration of response was not reached, but was estimated to be longer than 6.1 months. In addition, 43.4% of patients with severe pruritus experienced relief. The most common adverse effects included diarrhea, fatigue, and nausea, but most were of grade 2 or lower. Significant grade 3 side effects included pulmonary embolism (5%) and thrombocytopenia (5%). In this study, QTc interval prolongation was observed in three patients with no reported clinical sequelae, none of which were grade 3. There were no cases of infection. Another Phase II trial of vorinostat conducted in 33 patients with advanced or refractory CTCL at multiple doses demonstrated an ORR of 24% with a median time to response of 3 months and a median duration of response of 3.7 months. Forty-five percent of patients experienced relief of pruritus. In addition, analysis of lesion biopsies in responding patients demonstrated a shift in localization of phosphorylated STAT-3 from nuclear to cytoplasmic, suggesting that vorinostat may inhibit proliferation of CTCL cells by inactivating STAT3. Further in vitro work has shown that CTCL patients with high nuclear levels of STAT1 and pSTAT3 are resistant to vorinostat. Combination therapy has also been investigated, and PI3 K inhibitors have been found to synergize with vorinostat in reducing cell viability.

Romidepsin (depsipeptide, Istodax®) is another HDAC inhibitor recently approved by the FDA for patients with relapsed/refractory CTCL. Two Phase II trials were conducted in a total of 167 patients suffering from relapsed, refractory, or advanced CTCL. Romidepsin was administered intravenously at 14 mg/m² on days 1, 8, and 15 of a 28-day cycle. In both trials, the ORR was 34%, the complete response rate was 6%, the median time to response was 2 months, and median duration of response was longer than 12 months. The most common adverse effects were fatigue, nausea, vomiting, and anorexia. Severe adverse effects included leukopenia, lymphopenia, granulocytopenia, thrombocytopenia, and anemia. Earlier studies have shown that HDAC inhibitors may be associated with electrocardiographic abnormalities, such as QTc interval prolongation. In one trial, 9% of patients had QTc prolongation and 80% had asymptomatic T wave flattening or ST segment depression. The other trial had no patients with QTcF values >480 milliseconds or an increase of >60 milliseconds over baseline. It was also found that antiemetics might contribute to QTcF prolongation.

Panobinostat (LBH589) is another HDAC inhibitor that was shown in a Phase I trial to induce clinical responses in CTCL patients. Preliminary results of a Phase II trial of oral panobinostat have been reported. Panobinostat was administered at a dose of 20 mg on days 1, 3, and 5 weekly in bexarotene-treated patients and bexarotene-naïve patients. In 62 bexarotene-treated patients, 17.7% achieved a response. In 35 bexarotene-naïve patients, 12.1% achieved a response. Thrombocytopenia, neutropenia, pruritus, diarrhea, and hypophosphatemia were the most common grade 3 or 4 toxicities. Two patients had QTcF > 480 milliseconds and four had an increase in QTcF > 60 milliseconds from baseline.

Another HDAC inhibitor, belinostat (PDX101), is currently being evaluated in a Phase II trial of patients with relapsed/refractory T cell lymphoma that includes anaplastic large cell lymphoma and subcutaneous panniculitis-like T cell lymphoma. The treatment schedule is 1000 mg/m² intravenously on days 1–5 of a 21-day cycle. Of 19 evaluable patients so far, the ORR was 32% with a median time to response of 8 months.

Monoclonal antibodies

Monoclonal antibodies target tumor cells via cell surface markers upregulated on malignant T cells such as CD4, CD52, and CCR4. Zanolimumab (Hu-Max CD4) is a humanized anti-CD4 monoclonal antibody that has been shown in vitro to mediate antibody-dependent cellular cytotoxicity, primarily in CD4 + CD45RO + T cells. Zanolimumab also blocks T cell activation by macrophages in Pautrier’s micro abscesses via induction of inhibitory signaling pathways involving SHIP-1 and DOK-1. In two Phase II studies done in 47 patients with refractory early-stage and advanced-stage CTCL, zanolimumab was given intravenously at a weekly dose of 280 mg and 560 mg for early-stage patients and 280 mg and 980 mg for late-stage patients. The ORR was 56% in patients with mycosis fungoides treated with a high dose and 15% at a lower dose. In patients with Sézary syndrome, the ORR was 20% in patients treated with a high dose and 25% at a lower dose. Adverse events included skin inflammation (24%) and infections of the skin and upper respiratory tract (49%).

Alemtuzumab (Campath®), a humanized monoclonal antibody against CD52 surface antigen expressed on most malignant T cells, has been shown to mediate antibody-dependent cellular cytotoxicity, complement-mediated cell lysis, and apoptosis. A Phase II study was conducted in 22 patients with advanced CTCL at a dose of 30 mg intravenously three times a week. The ORR was 55% (32% complete response, 23% partial response). A greater effect was observed in patients with erythrodermic CTCL (69% ORR) than on plaque or tumor CTCL (40%). To investigate
this preferential effect on erythrodermic CTCL, another Phase II study was conducted in 19 patients with advanced refractory erythrodermic CTCL and found an ORR of 84%. Serious adverse events in these studies included infections and hematologic toxicity. Infections, occurring primarily in patients who had received three or more treatments, included cytomegalovirus reactivation, fever of unknown origin, herpes simplex virus reactivation, pulmonary aspergillosis, and Mycobacterium pneumonia. Hematologic toxicities included anemia, neutropenia, and thrombocytopenia. One study found adverse effects of congestive heart failure and arrhythmias following alemtuzumab treatment. However, several studies since have found no correlation with cardiac toxicity.

Chemotherapy

Conventional systemic treatments include chemotherapeutic agents and biologic immunomodulatory therapies. Gemcitabine (Gemzar®) and pegylated doxorubicin (Doxil®) are being used as newer initial single-agent chemotherapeutic choices. A Phase II trial of gemcitabine reported a 68% ORR in 25 patients with refractory advanced CTCL. In advanced untreated CTCL, gemcitabine was shown to result in a 75% response rate in 32 patients. Another study showed a response rate of 88% for pegylated liposomal doxorubicin.

Pralatrexate: targeted antifolate therapy

Methotrexate is the traditional antifolate used in therapy for lymphomas. It inhibits dihydrofolate reductase that converts dihydrofolate to tetrahydrofolate, which is required for synthesis of thymidylate and purine nucleotides involved in DNA and RNA synthesis. Pralatrexate (Folotyn®) belongs to a class of novel folate analogs, ie, the 10-deazaaminopterins, designed with greater affinity than methotrexate for receptor-reduced folate carrier, leading to improved drug internalization through membrane transport. It is also a better substrate for polyglutamylation than methotrexate, leading to greater intracellular retention and 10-fold greater cytotoxicity than methotrexate in lymphoma cell lines. Pralatrexate has been approved by the FDA for relapsed or refractory peripheral T cell lymphoma.

Preliminary results of a multicenter dose-escalation Phase II study in 54 patients with relapsed or refractory CTCL have been reported. The starting dose and schedule was 30 mg/m² intravenously once per week for 3 of 4 weeks. An optimal dose of 15 mg/m² for 3 of 4 weeks was defined, at which the ORR was 43%. The ORR was 50% at doses greater than 15 mg/m². Most common grade 1–2 adverse effects included fatigue, mucositis, nausea, edema, epistaxis, pyrexia, constipation, and vomiting. Grade 3 adverse effects included thrombocytopenia, neutropenia, leukopenia, and anemia. In another report of 12 patients with mycosis fungoides and large-cell transformation who were part of the multicenter PROPEL (Pralatrexate in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma) trial for patients with peripheral T cell lymphoma, the ORR was 58% via investigator assessment and 25% via independent central review. Combination therapy with bortezomib is currently under exploration.

Hematopoietic stem cell transplantation

The concept of high-dose combined chemotherapy followed by autologous bone marrow transplant or peripheral blood stem cell support has curative potential in various non-Hodgkin lymphomas, but experience in CTCL is limited. Autologous stem cell transplants have yielded disappointing results. Despite reported effective responses with complete response in most patients treated, relapses are frequent and may occur rapidly. Allogeneic hematopoietic stem cell transplantation (HSCT) with myeloablative conditioning regimens provides a graft-versus-tumor effect and avoids reinfusion of tumor cells, both of which are features lacking in autologous HSCT. However, myeloablation places the patient at high risk for infections and graft-versus-host disease, rendering HSCT difficult to use in the elderly and in those with multiple comorbidities. With the broadened use of nonmyeloablative reduced-intensity conditioning regimens, allogeneic HSCT may now be better suited for patients with CTCL. A retrospective study of 60 patients with advanced CTCL who received allogeneic HSCT and either reduced-intensity conditioning or myeloablative conditioning had a complete response rate of 60.5% and an overall survival of 54% at 3 years. Overall survival at 3 years in patients who received reduced-intensity conditioning was 63% compared with 29% in patients who received myeloablative conditioning. The median age of the patients was 46.5 years, indicating that allogeneic HSCT may be an effective treatment in younger as well as older patients. In another study of allogeneic HSCT with reduced-intensity conditioning and pre-treatment TSEBT for tumor debulking, 58% had a complete response, and overall survival at 2 years was 79%. Causes of mortality included sepsis, metastatic nonsmall cell lung cancer, and disease progression. Cord blood transplantation has also been attempted with some success in Japan in cases of failure or inability to attempt allogeneic HSCT.
Investigational therapies

Lenalidomide

Lenalidomide (Revlimid®), an analog of thalidomide, is currently approved by the FDA for treatment of myelodysplastic syndrome\textsuperscript{159} and refractory/refractory multiple myeloma.\textsuperscript{160} Its immunomodulatory properties, such as natural killer and T cell activation with induction of Th1 cytokine production and cytotoxic activity, along with alteration of the tumor cell microenvironment through antiangiogenic, antiproliferative, and proapoptotic properties, provided the rationale to use this agent in patients with CTCL.\textsuperscript{161} A Phase II trial in 35 patients with advanced/refractory CTCL showed an ORR of 32\%, a median time to response of 3 months, and a median duration of response of 4 months.\textsuperscript{162} The most common side effects were fatigue, lower leg edema, gastrointestinal symptoms, leukopenia, and neutropenia. Temporary tumor flares, characterized by an increase in size/number of skin lesions, tender swelling of lymph nodes, or increase in Sézary cell count, were noted in 25\% of patients following initial treatment. Data from this study also suggest that the immunomodulatory effects of lenalidomide might be associated with decreased Treg and CD4+ T cell numbers.

Oligonucleotides (nuclear acid therapeutics)

TLR agonists represent a novel approach to stimulate an effective antitumor immune response in patients with CTCL through augmentation of either dendritic cells or T cell effects. PF-3512676 (CPG-7909, ProMune\textsuperscript{®}) is a TLR-9-activating oligodeoxynucleotide and potent plasmacytoid dendritic cell stimulator\textsuperscript{163} that was recently shown in a dose-escalating Phase I trial to induce an ORR in 32\% of patients (three complete responses, six partial responses) with treatment-refractory stage IB to IV A CTCL.\textsuperscript{164} Twenty-eight patients received subcutaneous doses (0.08, 0.16, 0.24, 0.28, 0.32, or 0.36 mg/kg) once weekly for 24 weeks.

Proteasome inhibitors

Nuclear factor-kappa B (NF-kB) is an oncogenic transcription factor normally sequestered in an inactive state by the inhibitory I-kB molecule. Various oncogenic signals activate NF-kB via phosphorylation of I-kB, leading to its degradation via the 26S proteasome. Downstream targets of NF-kB include cIAP1, cIAP2, and Bcl-2.\textsuperscript{165} Bortezomib inhibits the 26S proteasome and therefore prevents degradation of I-kB and activation of NF-kB.\textsuperscript{166} It has been shown to induce apoptosis in CTCL via suppression of NF-kB-dependent antiapoptotic genes, cIAP1 and cIAP2, but not Bcl-2.\textsuperscript{165,167} A Phase II trial was conducted in 15 patients with relapsed/refractory cutaneous T cell lymphoma using a dose of 1.3 mg/m\textsuperscript{2} on days 1, 4, 8, and 11 every 21 days, for a total of six cycles. The ORR was 67\% (17\% complete responses, 50\% partial responses). Common adverse effects were neutropenia, thrombocytopenia, and sensory neuropathy.\textsuperscript{168} Currently, a Phase I trial is being conducted in patients with refractory T cell lymphoma using a combination of bortezomib and 5-azacytidine, a DNA methyltransferase inhibitor.

CCR4 antibody

KW-0761, a novel defucosylated humanized monoclonal antibody against CCR4, enhances antibody-dependent cellular cytotoxicity against malignant CTCL cells.\textsuperscript{169} In vitro studies of KW-0761 using mycosis fungoides and Sézary syndrome cell lines, primary mycosis fungoides and Sézary syndrome cells, and mycosis fungoides and Sézary syndrome mouse models showed not only significant antibody-dependent cellular cytotoxicity-mediated antitumor activity, but also a synergistic effect with IL-12, IFN-\alpha-2b, and IFN-\gamma. Phase I studies in adult T cell leukemia/lymphoma and peripheral T cell lymphoma have demonstrated an ORR of 31\%, with minimal adverse effects, consisting mainly of hematologic toxicities.\textsuperscript{170} Phase II studies are currently ongoing in patients with peripheral T cell lymphoma, CTCL, and adult T cell leukemia/lymphoma.

Conclusion

The significant strides that have been made in elucidating the mechanisms of pathogenesis in CTCL have allowed for the development of an extensive repertoire of targeted therapies. Patients with early-stage disease generally have an excellent prognosis and should be treated with skin-directed therapies. While no regimen has been proven to prolong survival in the advanced stages, immunomodulatory regimens are recommended initially to reduce the need for cytotoxic therapies. The existence of multiple mechanisms of oncogenesis in CTCL allows for a variety of mechanistic combinations and more individualized therapy. In more advanced stages of CTCL, treatment efforts should be made for palliation and improvement of quality of life. Unfortunately, other than allogeneic hematopoietic stem cell transplantation, there are no curative therapies for CTCL.

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