Pathogenesis and Therapy of Primary Cutaneous T-Cell Lymphoma: Collegium Internationale Allergologicum (CIA) Update 2020

Malgorzata Bobrowicz[a]   Christina Fassnacht[b, c]   Desislava Ignatova[b, c]
Yun-Tsan Chang[b–e]   Florentia Dimitriou[b, c]   Emmanuella Guenova[b–e]

[a]Department of Immunology, Medical University of Warsaw, Warsaw, Poland; [b]Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland; [c]Faculty of Medicine, University of Zurich, Zurich, Switzerland; [d]Department of Dermatology, Lausanne University Hospital (CHUV), Lausanne, Switzerland; [e]Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland

Abstract
Cutaneous T-cell lymphoma (CTCL) is a heterogeneous disease group of unknown etiology with a complex immunological background. As CTCL arises from T cells that have a vital role in the antitumor response, their therapy is largely aimed at reversing the immunological mechanisms leading to or manifesting during this malignancy. Early disease stages can be controlled with skin-directed therapy in most CTCL cases. Still, advanced CTCL has a dismal prognosis and warrants systemic therapy. Despite considerable progress in understanding the pathophysiology of the disease and the numerous systemic treatment options available, long-term remission rates with conventional treatments alone are still low. Allogeneic hematopoietic stem cell transplantation is currently the only curative option for advanced CTCL, including mycosis fungoides and Sézary syndrome.

The aims of this review is to summarize the recent findings on the immunology of this heterogeneous disease and to present the advances in its clinical management.

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Disease Prevalence and Subtypes

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of non-Hodgkin lymphomas arising from the malignant proliferation of skin-homing or skin-resident T cells [1, 2]. Although CTCL manifestation in children exists [3], most CTCL typically affect the elderly, with a median age at diagnosis of 55–60 years and an average number of 6.4 new cases per year and per million people [4].

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Malgorzata Bobrowicz and Christina Fassnacht contributed equally to this work.

Emmanuella Guenova
Department of Dermatology, Lausanne University Hospital (CHUV)
Ave. de Beaumont 29
CH–1011 Lausanne (Switzerland)
emmanuella.guenova@unil.ch

The 2 main subtypes of CTCL include the most frequent, i.e., mycosis fungoides (MF), accounting for approximately 60% of CTCL cases and 50% of all primary cutaneous lymphomas, and the rare leukemic variant Sézary syndrome (SS), representing around 5% of CTCL cases. The second most common group, representing approximately 25% of CTCL, is the group of primary cutaneous CD30+ lymphoproliferative disorders including primary cutaneous anaplastic large lymphoma and lymphomatoid papulosis [5]. Other CTCL subtypes are very rare [5, 6].

Clinical Manifestations

MF and SS originate from distinct CD4+ T-cell populations [7] and vary in terms of their prognosis as well as their clinical manifestations [8], with some overlapping symptoms such as chronic cutaneous lesions, associated with scaly rash, pruritus, burning, and sometimes pain [9] with recurrent infections, thus having a significant impact on the quality of life due to subsequent psychological problems and sleep disorders [10, 11]. Most patients with MF present a prolonged, indolent clinical course with initial skin involvement and clinical presentation depending on the stage at diagnosis [12]. Of all MF patients, 71.5% are in an early stage and 28.5% are in an advanced stage of the disease, and progression to a higher stage of the disease occurs in 9.7–11.6% of patients [13]. MF restricted to the skin progresses from a persistent patch stage with finely scaling lesions to a plaque and tumor stage, typically in sun-protected areas over years [8]. Extracutaneous disease initially involves regional lymph nodes and is mostly present with extensive skin involvement with tumors or erythroderma.

In CTCL leukemic variants, including SS and a portion of advanced-stage MF, malignant CD4+ T cells accumulate in the peripheral blood and visceral organs, with a subsequently dismal prognosis. SS is defined as an aggressive leukemic CTCL clinically defined by the triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T cells in the skin, lymph nodes, and peripheral blood (Sézary cells) [8]. Cutaneous lesions include erythroderma, plantar and palmar keratoderma, onychodystrophy, ectropion, and diffuse alopecia [14].

Etiology

The etiology of CTCL remains largely unknown. Viruses, such as human T-cell leukemia virus type 1, have been previously suggested as drivers of the disease [15], but recent studies do not present enough evidence to support the viral hypothesis in the pathogenesis of MF and SS [16]. Antigen-driven T-cell lymphoproliferation or dyscrasia following medication use [17], as well as genetic factors, i.e., HLA class II alleles predisposing to the disease [18], have been reported. Recent attempts to profile the genomic landscape of CTCL have demonstrated its high heterogeneity. Although the pathogenesis of the disease cannot be attributed to a small subset of well-defined somatic mutations, copy number variations, fusion proteins, and somatic mutations in diverse cellular and signaling pathways might contribute to the pathogenesis of the disease [19–22]. Those include alterations in factors functioning in epigenetic regulation, DNA damage response, cell cycle control, programmed cell death, and T-cell receptor (TCR) signaling, as well as nuclear factor (NF)-κB and Janus kinase (Jak)/signal transducer and activator of transcription (STAT) pathways [19, 20, 23–26]. Next to those intrinsic drivers, also extrinsic drivers, most commonly *Staphylococcus aureus* (SA) and its toxins, are under debate [27]. However, epidemiological studies could so far not reliably identify environmental exposure as a trigger for the disease [28].

Malignant T-Cell Heterogeneity

As the name indicates, CTCL is a disease of T cells, although MF and SS appear to have their origin in different T-cell subtypes [7]. Based on flow cytometry analysis of lymph node or skin-homing molecules and differentiation markers, MF has been characterized as a malignancy of skin-resident effector memory T (T_{EM}) cells (CCR4+ and CLA+), while SS cells present a phenotype of central memory T (T_{CM}) cells (CCR7+, CD27+, and L-selectin+) [7]. These findings explain some of the differences in the clinical manifestation of the disease. T_{EM} cells are skin-resident stationary polarized effector cells producing high amounts of inflammatory cytokines [29] that result in a skin-limited presentation in the form of patches, plaques, or tumors that remain stable for years. A progressive disease with the involvement of blood, lymph nodes, and viscera develops only in a small subset of patients [2]. In contrast, T_{CM} are highly proliferative and actively recirculate between the blood, lymph nodes, and skin [2].

Differences in the genetic background of T-cell precursors in these CTCL subtypes have been further proven by comparative genomic hybridization and gene expression analyses [22, 30, 31]. However, malignant T cells differ not only between CTCL subtypes but also between
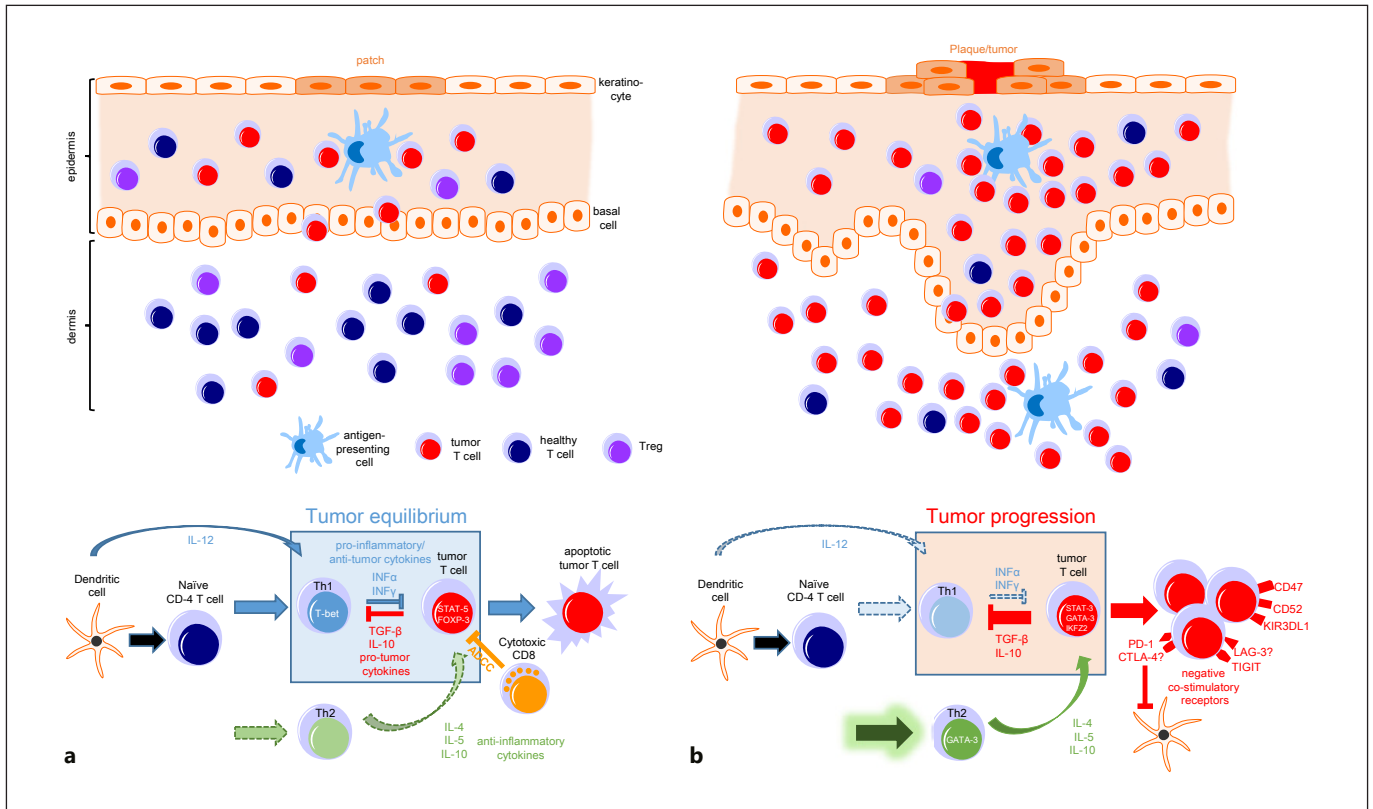
Fig. 1. Immune responses in early- and advanced-stage CTCL. **a** Early-stage CTCL. Upper panel: schematic illustration of the cellular composition in patch-stage disease. Small populations of tumor T cells are present mostly in the epidermis and are held in check by surrounding healthy T cells and regulatory T cells. Lower panel: immunosurveillance mechanisms are partially intact, the antitumor Th1 immune response can control tumor progression, leading to a tumor equilibrium. **b** Advanced-stage CTCL. Upper panel: schematic illustration of the cellular composition in plaque/tumor stage disease. The number of infiltrating tumor T cells is largely increased and present now also in the dermis, while the number of healthy T cells and T regulatory cells is decreased. Lower panel: immunosurveillance of the tumor is largely defective. A skewed Th1 immune response and an increased Th2 response, among other mechanisms, lead to immune escape of tumor cells and allow tumor progression.

patients with the same disease. In a cohort of SS patients it was observed that not all malignant T-cells were characterized by the T_{CM} phenotype, but malignant cells from a subgroup of SS patients (18 out of 47 patients) expressed markers of a naive, more stem cell-like phenotype, such as high levels of CD45RA [32].

Finally, it has become evident that malignant T-cells show a high intrapatient variability, and follow-up data of SS patients suggests also an evolution in the phenotype of SS cells, demonstrating their plasticity [32]. Single-cell RNA sequencing combined with flow cytometry showed a high heterogeneity of classical T-cell markers within individual patients, with a common cluster of only 5 proteins (S100A4, S100A10, IL7R, CCR7, and CXCR4) [33].

Single-cell RNA sequencing of SS cells suggests also the existence of cases with a shift from a T-regulatory-like phenotype (characterized by FOXP3 expression) to a more central memory phenotype (characterized by the expression of a major Th2 driver – GATA3 or IKZF2) in malignant CD4+ cells [34]. In line with this finding, FOXP3 could be an important factor to predict early disease in CTCL, along with another 19 genes suggested to correlate with different CTCL stages [34]. Nevertheless, the role of Treg cells in the pathogenesis of SS is still controversial [35–37]. Some clinical cases in which CTCL appeared with the phenotype of malignant proliferation of Tregs have been observed [38]. Also, a recent study by Borcherding et al. [34] confirmed the presence of CD25-FOXP3+ tumor cells in a subset of SS patients. Of interest, in murine modes, an inadequate CD25 expression guarantees Treg plasticity and their differentiation into a Th phenotype depending on the cytokine milieu [39]. Hence,

the CD25– FOXP3+ population may be an intermediate state of SS cells as well. Recent analyses suggest a marked decrease in the number of T_{CM} following HDAC inhibition [33] which may be attributed to an open chromatin state leading to FOXP3 activation [40].

Antitumor Response and Immune Evasion

Early-Stage CTCL: Equilibrium Phase

The patient's immune system has an important influence on the tumor fate. Many MF patients can have indolent disease over years, most likely presenting an equilibrium phase where the adaptive immune response can still control tumor outgrowth [11]. Early-stage skin lesions (stages IA to IIA) are infiltrated by a small number of malignant T cells surrounded by reactive immune cells, including large numbers of activated CD8+ T cells and T helper 1 (Th1) cells, resulting in the establishment of cell-mediated antitumor responses and secretion of cytotoxic molecules, including the proinflammatory cytokines interferon (IFN)-α and IFN-γ (Fig. 1a) [41–46]. In early-stage CTCL, the Th1 phenotype is maintained by the expression of signal transducer and activator of transcription 4 (STAT-4) and interleukin (IL)-12 signaling via JAK2/TYK2 [47].

Advanced-Stage CTCL: Tumor Progression Phase

The escape from immune recognition can lead to tumor progression as observed in advanced-stage CTCL (stages IIB to IVB) with a large increase in infiltrating tumor T cells presenting on the skin with plaques and tumors (Fig. 1b). During disease progression, the expression of Th2 markers (e.g., GATA-3) and cytokines (e.g., IL-4, IL-5, and IL-10) increases, whereas the expression of Th1 transcription factors, such as T-cell-specific T-box transcription factor (T-bet), IFN-γ, STAT4, and IL-12 decreases [48, 49]. What shifts the balance in favor of tumor progression remains to be largely unknown in CTCL. One contributor might be mutations in the JAK/STAT pathway, making it persistently active in cancer T cells [49]. In early disease, there is constitutive activation of STAT5; in later disease there is activation of STAT3. STAT-5 via miR-155 reduces STAT4 expression, which is critical for the Th1 phenotype and thereby contributes to a Th1 to Th2 switch [49]. Moreover, STAT5 is known to be involved in the transcription of antiapoptotic proteins (bcl-2 and bcl-xl), cell cycle genes (cyclin D and c-myc), and IL-4 cytokines and its activation could be therefore an important driver of tumor cell proliferation [50, 51].

In addition to the dominance of the Th2 phenotype in advanced stage CTCL, several types of immune cells have been shown to contribute to a state of immune evasion of the tumor cells. Among them are subpopulations of dendritic cells (DC; immature CD209/DC-DIGN+ DC) [52] and subpopulations of CD4+ and CD8+ T cells with a high expression of immune checkpoint inhibitors [53]. Moreover, as already mentioned, also an impaired IL-12 production by DC contributes to the Th2 switch [54].

A clinical characteristic of advanced stage CTCL encompasses the susceptibility to infections as a consequence of impaired antigen-specific T-cell responses and decreased CD8 cytotoxic response [55]. The susceptibility to infections together with peripheral eosinophilia and high IgE and IgA levels further confirms a Th2-driven immunological process [55]. Interestingly, high IgE to environmental and food allergens in Sézary patients has been associated with a lower survival rate [56]. Therapies targeting the Th2 phenotype that would reinvert it into a Th1 immunological response hold potential for improving both the anticancer and the antipathogen response [41].

The presence and role of natural killer (NK) cells in CTCL skin lesions is still under debate. CTCL cells have been demonstrated to be susceptible to NK-induced killing in vitro [57]. Recently, an analysis of NK cells in peripheral blood showed no significant difference in the number of NK cells in CTCL versus healthy individuals [58]. This is in contrast with previous reports of decreased NK cell numbers in SS patients that suggested that their function may be increased by Toll-like receptor (TLR) stimulation [59]. On the other hand, higher numbers of circulating NK cells have been correlated with a poorer prognosis both in MF and in SS [58] and related to findings in another Th2-mediated disease, i.e., atopic dermatitis (AD), where NK dysregulation contributed to AD pathogenesis [60]. Although the reason for these findings is not entirely clear, they suggest that the existence of the inhibitory mechanism of the CTCL microenvironment has a significant role in suppressing the anti-tumor activity of NK cells in vivo. One such factors may be chronic IL-15 stimulation leading to an exhaustion state of NK cells, defined as their hyperactivation together with impaired recognition of malignant cells [58]. However, the involvement of NK cells in providing an antitumor response in the skin remains controversial, as NK cells have been described to be present in the skin in scarce amounts [61, 62]. The effectiveness of rituximab (anti-CD20 mAb) in the therapy of primary cutaneous B-cell lymphoma indicates that NK cells in the skin have valid antibody-de-

pendent cell-mediated cytotoxicity (ADCC). However, in a phase 3 clinical trial, the reported response rate (RR) of mogamulizumab (anti-CCR4 mAb) was only 28% despite the high CCR4 expression in the study cohort [63]. Also, the RR in the skin was much lower compared blood. Impaired ADCC may also contribute to the inefficacy of anti-CD52 mAb (alemtuzumab) in MF [64, 65].

Neutrophils may also contribute to CTCL pathophysiology, as hyperactivated neutrophils are found in peripheral blood of CTCL patients (even in early disease) and the secreted IL-8 and LTB4 contribute to skin inflammation [66]. Moreover, an increased number of myeloid-derived suppressor cells (MDSCs) in comparison to healthy subjects has been observed in both MF and SS and a decrease in their numbers has been noted after successful therapy [67–69].

Therapy

Treatment of CTCL depends on the stage of the disease and the general condition of the patient. Early disease stages of MF (IA-IIA) can be controlled with skin – directed therapy, such as topical steroids, light treatment and radiation [4, 70]. Systemic treatments, such as retinoids and IFN-α have been recommended as second-line treatment of MF stages IA, IB and IIA [71]. The 5-year survival for these patients is around 90%, significantly better compared with 30%–50% for advanced disease (IIB–IVB) [72]. Chemotherapy agents, such as monochemotherapy (gemcitabine, pegylated liposomal doxorubicine) and polychemotherapy, as well as newer systemic agents (brentuximab-vedotin and mogamulizumab) are recommended in advanced disease stage. Large cell transformation in histology, expression of CD30 and folliculotropic subtype of MF have been reported to have a more aggressive course and poorer prognosis. Although rare cases of CD4- CD8+ , CD4- CD8- , or CD4+CD8+ immunophenotypes have been described in MF, these differences in phenotype do not affected the prognosis of the disease [73]. However, a phenotypic switch from CD4+ to CD4- in the lesion has been suggested a portend of poor outcome [74].

SS is associated with a poor prognosis and overall survival rates varying from 7.5 to 22.4 months [75]. Apart from conventional treatments (e.g. extracorporeal photopheresis (ECP), light treatment (PUVA), retinoids, IFN-α, low dose methotrexate and polychemotherapy), small-molecule inhibitors e.g. histone deacetylase inhibitors (HDACi) and monoclonal antibodies (mAbs) are current-

ly being explored as therapeutic options in SS [76, 77]. A comprehensive review on investigative drugs in CTCL has been published recently [78]. Despite their initial moderate to good response to most treatments, SS patients often develop resistance to treatment in the course of the disease [79]. Selection of more robust and aggressive tumor clones has been hypothesized as one possible driver for resistance; e.g. in a small cohort of SS patients, tumor cell subpopulations were heterogeneous and showed different sensitivity to HDACi [33]. Also, although no single common driver mutation has been identified, novel findings demonstrate aberrant functioning of cell division mechanisms in CTCL that lead to genetic instability and possible escape to treatment [80]. Further, the role of STAT3 activation in conferring resistance in both SS and advanced-stage MF has become clearer [81, 82]. And finally, SS cells have been shown to display resistance to apoptosis when chromatin remodeling is defect, such as in SNF5- and SATB1-deficient cells, or when Fas-mediated apoptosis is defect [83, 84]. If and how exactly these mechanisms contribute to treatment resistance in SS cell subpopulations has yet to be addressed in detail. Taken together, despite the numerous systemic treatment options available, long – term remission rates with conventional treatments alone are still low and allogeneic hematopoietic stem cell transplantation (alloHSCT) is currently the only curative option in advanced MF/SS [85, 86].

Thorough reviews analyzing the therapeutic options available for CTCL have been lastly identified in the literature [70, 85, 87, 88]. Herein, we summarize the recent advances in the immunotherapies of CTCL.

Recent Advances in Immunotherapies of CTCL

ECP and PUVA
Both extracorporeal photopheresis (ECP) and psoralen plus ultraviolet A (PUVA) consist of the systemic or local application of 8-metoxypsolaren and subsequent photoactivation resulting in apoptosis of malignant lymphocytes [89–92]. However, despite the established use in the management of CTCL, their mechanism of action is still not sufficiently investigated. While PUVA is applied to patients with earlier stages of CTCL and skin involvement only, ECP is used mainly in erythrodermic patients with blood involvement [93]. PUVA induces remission lasting up to 10 years in 72% of MF patients [2, 94] and is described to have an immunomodulatory effect i.e. a shift from Th2 to Th1 phenotype [95]. A recent study by Vieyra-Garcia et al. [96] shed new light on the mechanisms

beyond PUVA efficacy in CTCL. The authors have demonstrated a switch from a Th2 with CCL18 overexpression, to a Th1 phenotype characterized by CXCL9, CXCL10, and CXCL11 expression. Moreover, they have shown that while in low-burden disease the efficacy of PUVA results in the reduction of the number of malignant T-cells, in high-burden disease it relies mostly on the recruitment of clonal cytotoxic T cells. The study identified the c-Kit+OX40L+CD40L+ DC as the major drivers of inflammation and clonal expansion of malignant T cells due to their pro-survival impact and suggested targeting c-Kit, OX40, and CD40 signaling may be a novel therapeutic option in the treatment of MF.

ECP induces response rates of approximately 60%, with complete responses of 14–26% [89, 97] that can be further improved when combined with other immunomodulatory agents, such as IFN-α or systemic retinoids [89, 98]. The immunomodulatory effect of ECP is thought to rely on the induction of monocyte differentiation to DC that are capable of phagocytosing and efficiently presenting tumor antigens [99, 100]. Moreover, a shift from Th2 bias to a Th1 proinflammatory phenotype has been reported [90]. Recently, there has been considerable interest in defining the role of NK cells in the success of ECP. Recent studies have reported a significant increase in the percentage of CD56+dim NK cells characterized by a high cytotoxic potential 3 months after the start of therapy [20]. Interestingly, Mundy-Bosse et al. [58] reported that increased NK cell cytotoxicity and higher NK-cell numbers before ECP were associated with decreased short-term survival.

Monoclonal Antibodies

Mogamulizumab (Anti-CCR4)

Mogamulizumab, a glycol-engineered mAb targeting chemokine receptor type 4 (CCR4) with an increased affinity to FcγRIIIa (CD16) and enhanced ADCC [101], was approved in August 2018 for patients with relapsed or refractory, advanced CTCL with at least 1 prior systemic therapy [63]. Apart from the clinical efficacy, patients treated with mogamulizumab reported an improvement in their quality of life, including skin pain and fatigue [63]. Mogamulizumab is generally well-tolerated; however some skin-related toxicities due to the induction of autoantibodies recognizing human keratinocytes or melanocytes that induce complement-dependent cytotoxicity have been reported [102]. Of note, targeting CCR4 may also result in the depletion of nonmalignant Tregs, thus leading to or aggravating autoimmune disorders [103]. In this way, it also increases the risk of graft-versus-host dis-

ease following allogeneic bone marrow transplantation [104], which should be therefore delayed by at least 50 days from the administration of the last dose [105].

Immune Checkpoint Inhibitors

Based on the increased response rates associated with targeting of negative immune regulators through mAbs, also known as immune checkpoints inhibitors (ICI), in a wide spectrum of malignancies, including melanoma, there is considerable interest in applying these targets in the management of CTCL [87]. The particularity of CTCL in the context of implementation of ICI relies on the fact that the tumor itself arises from CD4+ T cells, a population of lymphocytes responsible for priming of the cytotoxic response. Increasing evidence suggests that in CTCL both CD4+ and CD8+ cells have characteristics of immune exhaustion [53, 106, 107], and therefore targeting immune checkpoints would have implications on the functionality of both helper and cytotoxic T cells. One immune-inhibitory axis is the programmed death (PD-)1 axis, binding to its ligands PD-L1/L2. PD-1 expression has been shown to be high in the blood and skin of SS patients [108, 109] and has already been proposed as a factor responsible for drug resistance in SS [110]. A phase 2 clinical trial of the anti-PD1 mAb pembrolizumab in heavily pretreated advanced-stage MF and SS patients reported an ORR of 38%, with a 1-year progression-free survival of 69% and a duration of response of 64 months [111, 112]. Moreover, there are also ongoing trials targeting PD-L1, using anti-PD-L1 mAbs, i.e., atezolizumab (NCT03357224) and durvalumab (NCT03011814).

A recent analysis investigating PD-1 expression in SS showed a high PD-1 expression on tumor T cells compared to nontumor CD4+ T cells from SS patients or to normal CD4+ cells from healthy individuals [113]. In contrast, PD-L1 showed a decreased expression on tumor T cells, while PD-L2 expression is low and did not show any significant differences between groups. This is in line with other studies [114], where PD-L1 showed a high expression in the tumor environment, particularly in monocyte-derived compartments, where it was expressed by 73% of cells. Also a recent study by Querfeld et al. [53] showed high PD-L1 levels in DC émigrés from the skin but a low expression by T cells themselves.

While PD-1/PD-L1 ICI have gained much interest in the therapy of CTCL, much less is known about the expression of other immune receptors. In an analysis of CTCL skin samples, Querfeld et al. [53] observed a higher expression of CTLA-4 on both CD4+ and CD8+ T

cells. In another study no significant differences were found in CTLA-4 expression in CD4+ malignant versus bystander T cells in SS patients and healthy controls [115]. However, as the combination of anti-PD-1 (nivolumab) with anti-CTLA-4 showed no benefit compared to nivolumab alone [116], there are no active or recruiting clinical studies testing the efficacy of CTLA-4 targeting in CTCL. A recent analysis [115] of a panel of checkpoint inhibitors in a small cohort of SS patients revealed a significant upregulation of FRCL3 and TIGIT expression, which is in line with the previous reports [117, 118], together with a reduced expression of LAG-3 on CD4+ tumor cells. As several advanced clinical studies address TIGIT as a target molecule, it may also be of interest in CTCL. Interestingly Querfeld et al. [53] observed increased LAG-3 expression in lesional MF skin samples, which may be explained by the fact that MF and SS arise from distinct T-cell subsets [7]. Further, a hitherto nondemonstrated overexpression of BTLA on CD4+ cells in SS has been reported [115]. This is of possible interest, as BTLA blockade would arrest T-cell proliferation and can be therapeutically targeted by a specific fragment (HVEM 26–28) [119]. However, no in vivo studies have been conducted so far. As immune checkpoints have nonredundant roles in cancer progression, other emerging regulatory molecules (TIM-3, CD96 [TACTILE], and PD-1H [VISTA]) may be of interest in CTCL, too.

CD47

CD47 is highly expressed on Sézary cells in the peripheral blood and skin and correlates with a worse overall survival [120]. Inhibiting the binding of CD47 to its ligand, SIRPa activates both innate and adaptive antitumor responses by promoting phagocytosis and subsequent activation of CD8+ T cells [reviewed in 121]. Targeting CD47 with TTI-621 not only blocks the "do-not-eat-me signal" of CD47 but it also enhances phagocytosis of tumor cells by monocytes. The data gained in 2 phase I trials suggest its satisfactory activity combined with a good safety profile [120, 122].

Alemtuzumab (Anti-CD52)

Alemtuzumab is a monoclonal Ab directed against the surface glycoprotein CD52. CD52 expression on malignant T cells has been shown in 14 out of 16 CTCL cases by flow cytometry [123]. In several clinical studies, alemtuzumab appears to reach better responses in Sézary patients, with an ORR of 81%, as compared to MF patients, with an ORR of 29% [124]. A retrospective study of 39 advanced CTCL patients also showed long-term remission in Sézary patients but not in MF patients [65]. The treatment is associated with a high toxicity, but this can be lowered by subcutaneous administration (as compared to intravenous) and lower doses of the antibody. Despite a good response rate in Sézary patients, it is not approved anymore for CTCL treatment. Currently, there is an ongoing phase I study using a combination treatment of IL-15 and alemtuzumab in different T-cell leukemia and lymphoma conditions (NCT02689453).

KIR3DL2 Targeting

KIR3DL2, also called CD158k, is overexpressed by transformed advanced MF and SS cells correlating with the disease stage and large cell transformation [125] as well as a shorter survival [126]. IPH4102, an anti-KIR2DL2 humanized IgG1 mAb, effectively induces ADCC and immunophagocytosis [127], delays tumor growth, and improved the overall survival in a xenograft mouse model. The results of a phase I study in MF and SS patients (NCT02593045) demonstrated a confirmed global overall response in 16 of 44 patients (36.4%; 95% CI 23.8–51.1), and, of those, 15 responses were observed in 35 patients with SS (43%; 95% CI 28.0–59.1) [128]. Moreover, a phase II trial of IPH4102 alone or in combination with chemotherapy in patients with advanced T-cell lymphoma (TELLOMAK) (NCT03902184) is currently recruiting.

Chimeric Antigen Receptor-Based Therapies

Given their success in the treatment of B-cell malignancies, chimeric antigen receptor (CAR)-modified lymphocytes raise interest as a therapeutic option in CTCL. However, their use poses some considerable issues. First of all, there is a lack of specific targets expressed uniquely on malignant T cells. This results in 2 different concerns. One is that, when using a specific target for a tumor (sub)population, not all malignant cells are affected by the treatment and relapse of the disease occurs. The other is that, when using a more broadly expressed marker, targeting also of healthy T cells can occur, which can lead to life-threatening T-cell aplasia. While the first concern is difficult to solve, unless a unique marker expressed by all malignant cells is discovered, the second concern could be overcome by a transient CAR expression or expression of suicide genes allowing for reconstitution of T cells. By now CD4, CD5, CD7, CD30, CD37, CCR4, and TCR β chains (TRBC1/TRBC2) have been tested as possible targets of CAR-based therapies [reviewed in 129]. An alternative to targeting T cells is the application of CAR-transduced NK cells. This may offer an alternative as it eliminates the

phenomenon of fratricide, i.e., mutual killing of CAR-expressing cells due to shared T-cell antigens [129].

Cytokines
Interferons

Next to IFN-α, which is an approved and recommended treatment for MF and SS [130], IFN-γ has emerged as a novel option for the patients who have failed IFN-α. IFN-γ abrogates the Th1/Th2 bias inducing a Th1-dominated tumor microenvironment and stimulates macrophages, DC, and cytotoxicity, mediated by CD8 T cells and NK cells [131]. As demonstrated by a small-scale study by Kaplan et al. [132], who treated 16 MF and SS patients with IFN-γ, 31% of patients had an objective partial response. None of the patients showed a complete response. A subsequent small-dose-escalating study by Dummer et al. [133] demonstrated the therapeutic effect of intratumoral injections of TG1042 (a third-generation, nonreplicating human adenovirus vector containing a human IFN-γ cDNA insert). The observations included 9 patients (CTCL, $n = 7$; CBCL, $n = 2$) injected with the following doses of TG1042: 3×10^9, 3×10^{10}, and 3×10^{11} total particles. A local clinical response was observed in 5 of the 9 treated patients (3 patients with a complete response and 2 patients with a partial response). Three patients reported a complete systemic response, represented by clearance of noninjected skin lesions. The duration of the clinical response was on average 3 months (range 1–6 months) and only grade 1 and 2 adverse events were reported [133].

Interleukin-12

IL-12 is a Th1-promoting cytokine produced by the antigen-presenting cells. It is a potent inducer of IFN-γ. IL-12 boosts NK cell activity and cytotoxic T-cell responses in CTCL [134]. As discussed before, a Th2-dominant cytokine milieu and a reduced production of Th1-inducing cytokines such as IFN-γ and IL-12 are a hallmark of immune evasion in advanced MF and SS [135]. In vitro data have shown increased lysis of malignant cells derived from SS patients when cultured with IL-12, providing additional evidence of the role of cytokines in antitumor immune function [134]. The therapeutic effect of IL-12 administration was tested in a small-scale ($n = 10$) phase I trial using 50–300 ng/kg IL-12. The study cohort included patients with MF and SS, stages T1 to T4. Unfortunately, the observations in SS patients were scarce because 2 of the 3 SS patients withdrew from the treatment. Overall, 20% of the patients showed a complete response, 20% showed a partial response, and the remaining patients had no response or a local response.

TLR Agonists

TLR are key players in innate immunity. TLR are predominantly expressed by DC and macrophages and recognize pathogen antigens in the microenvironment [136]. Once bound to their ligand, they induce antigen presentation and cell proliferation and cause surface upregulation of costimulatory molecules on the antigen-presenting cells, leading to T cell activation and increased cytotoxicity [137]. The therapeutic targets addressed in CTCL are TLR7 and TLR8, which bind viral RNA particles, and TLR9, which binds bacterial and viral DNA.

Imiquimod (TLR 7 Agonist)

TLR7 is expressed on plasmacytoid DC (pDC) [138]. Targeting TLR7 with a synthetic ligand, i.e., imiquimod, induces the production of proinflammatory cytokines, i.e. IFN-α, which induces a Th1 type immune response and shift towards cell-mediated immunity. There are several case reports and case series describing the efficacy of imiquimod treatment in CTCL patients [139–145]. Summarized results of the studies demonstrate that 71% of the patients have a complete response and 17% stable disease. Despite the promising results, imiquimod is not approved for use in CTCL because larger trials are necessary to evaluate its efficacy and safety in MF and SS.

Resiquimod (TLR7 and TLR8 Agonist)

Resiquimod binds to both TLR7 and TLR8. Despite their structural similarity, the 2 receptors differ in their signaling, and their activation leads to secretion of different cytokines. The TLR7 agonist activates predominantly pDC, inducing the production of IFN-α and IFN-regulated chemokines such as IFN-inducible protein and IFN-inducible T-cell α chemoattractant. The TLR8 agonist activates mDC, monocytes, and MDC to secrete TNF-α, IL-12, and MIP-1α [146]. In summary, TLR7 activation results in a 5–10 times greater production of IFN-α, whereas TLR7/8 stimulation increases TNF-α and IL-12 levels approximately 10 times. A phase I clinical trial with 12 early-stage patients (from IA to IIA MF) illustrated a 17% complete response rate and a 75% partial response rate in patients. Moreover, the dose escalation correlates with a better response [147]. The elevated after-treatment levels of TNF-α, IL-12, and IFN-γ induce the cytotoxic function of CD8 and NK cells and partial or complete reduction of the clonal malignant T cells in skin biopsies and correlate positively with treatment response.

TLR9 Agonist

TLR9 is an intracellular receptor expressed on numerous immune cells and it is activated by unmethylated CpG sequences found in bacterial or viral DNA. Its binding initiates the release of proinflammatory cytokines such as type I IFN and IL-12 [148]. In a phase 1/2 study by Kim et al. [149] 15 MF patients received intratumoral injections with TLR9 agonist CpG oligodeoxynucleotides combined with localized radiation. The combination of TLR9 agonist treatment and radiation was chosen because local radiation increases the number of available tumor antigens for pDC, which in parallel are primed by unmethylated CpG sequences. The overall response rate is approximately 36% with a median response duration of 7 weeks.

Antibiotics

A diminished diversity of skin microbiome with a tendency toward increased colonization with SA has been reported in both MF and SS [150, 151]. It has been suggested that SA enterotoxins stimulate a reciprocal cross-talk between nonmalignant and malignant T cells resulting in IL-2-dependent proliferation of the malignant clone [152] and that interaction of T cells with the bacterial microenvironment may accelerate disease progression by promoting STAT signaling [153]. Thus, microbiome targeting may be a therapeutic strategy. Indeed, a recent small clinical study by Lindahl et al. [154] demonstrated that a short-term aggressive treatment with a SA-targeting antibiotic regimen resulted in a marked long-lasting clinical improvement in advanced-stage CTCL patients [154], leading to a decrease in the proliferation of malignant cells, STAT3 signaling, and the expression of CD25. These observations encourage the conduction of studies combining the targeting of SA together with STAT signaling [155].

Outlook

CTCL is a rare skin lymphoma arising from malignant T-cell homing to or sessile in the skin. Both intrinsic and extrinsic factors may play a critical role in the pathophysiology of CTCL and cutting-edge research is currently focused on how increased levels and/or overactivation of key molecules, such as STAT3, GATA3, CCR4, and KIR3DL2, contribute to the initiation and progression of the disease. The extensive research performed in recent years has greatly advanced our understanding of CTCL and its impact on patient care and quality of life.

Naturally occurring molecules and genes, involved directly in or acting as surrogate parameters for active pathophysiological disease processes, if easily detectable, are convenient for use as biomarkers, disease-classifying molecules, or treatment targets. However, the heterogeneity of CTCL renders the detection of common markers and/or therapeutic targets difficult. Novel technologies and large-scale data generation combined with analytical approaches supported by artificial intelligence are expected to deliver the necessary knowledge and allow personalized medicine for the domain of CTCL.

The rarity of the diseases of the CTCL group necessitates an international collaborative effort to successfully accomplish high-evidence clinical research. In the last few years, the set-up has been established and successfully applied for at least 2 large prospective randomized clinical trials.

Conflict of Interest Statement

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Author Contributions

All of the authors searched for and collected literature data and participated in the writing and approved the final version of this paper.

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