Review Article

Immune evasion and current immunotherapy strategies in mycosis fungoides (MF) and Sézary syndrome (SS)

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Abstract: Mycosis fungoides (MF) and Sézary syndrome (SS) are two well-characterized skin limited and leukemic subtypes of cutaneous T-cell lymphoma (CTCL), respectively. Progressive global immune dysfunction and a multitude of specific immunological abnormalities have long been recognized as features of MF and SS. Therefore, a variety of immune-based therapies have been explored and used in the clinic for decades in the attempt to restore the immune imbalance in these malignancies. With recent advances in the development of novel immunotherapies in cancer treatment, new treatment modalities have emerged to complement the existing repertoire. Herein, we provide a comprehensive review of immune evasive mechanisms in MF/SS and summarize the established and emerging immunotherapies for these malignancies. We explain the underlying mechanisms of these immune-based therapies and derive recommendation from results of major clinical trials.

Keywords: Cutaneous T-cell lymphoma (CTCL); mycosis fungoides (MF); Sézary syndrome (SS); immunotherapy; immune evasion

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Introduction

Cutaneous T-cell lymphomas (CTCL) are a family of primary extranodal lymphoid neoplasms that develop from the malignant transformation of post-thymic skin-homing T cells. Mycosis fungoides (MF) is the most common form of CTCL, characterized by an aberrant and excessive proliferation of CD4 T cells in the skin. Clinically, MF typically presents as cutaneous patches, plaques, or tumors, without extracutaneous involvement. In contrast, Sézary syndrome (SS) is a more advanced subtype of CTCL that manifests with erythroderma, generalized superficial lymphadenopathy, and a high burden of circulating malignant T cells (1). Although early-stage MF patients have an indolent course, those with advanced stages and SS patients have compromised survival (2,3).

None of the existing therapies for CTCL, with the possible exception of allogeneic hematopoietic stem cell transplantation (HSCT), has been shown to produce long-term durable remissions that could be defined as "cure". Hence, the current goal of treatment is to induce remissions across the anatomic compartments affected by the disease (skin, blood, lymph nodes, and viscera), relieve disease-related symptoms, and halt stage progression. Recently,

there has been a growing interest in treatments that leverage the immune system and enhance cell-mediated immunity in cancer patients. While certain immunomodulatory treatments have been used for decades in the treatment of MF/SS, newer agents have been introduced in recent years. Immunotherapy, defined by an enhancement of the anti-tumor immune response, encompasses a range of treatment modalities for MF and SS. With this review we will examine the clinically tested immunotherapies for the treatment of MF and SS, as well as ongoing research on potential new targets for treatment.

Anti-tumor immune response in CTCL

The concept of tumor immunogenicity was first postulated by Burnet in 1970, who proposed that malignant cells express traits recognized by innate and adaptive immune cells (4). MF is an immunogenic malignancy and there is evidence that it can elicit an antitumor immune response (5,6). While the specific immunogenic characteristics of malignant CD4 T cells in MF/SS remain to be characterized, the presence of high numbers of CD8 cytotoxic T cells along with dermal dendritic cells in early MF lesions is suggestive of an antitumor response (5,6). In fact, the number of tumor-infiltrating CD8 T cells in MF lesions correlates with a more favorable outcome (7). Furthermore, enhanced CD8 T cell activation and increased expression of natural killer (NK) cell antigens in the blood of patients with early CTCL imply a systemic anti-tumor response in early stages (8). In line with this, Mundy-Bosse *et al.* demonstrated that CTCL patients had significantly higher levels of NK-cell cytotoxicity compared with normal donors. However, the *in vivo* mechanisms regulating the numbers and function of circulating NK cells in patients with MF/SS are complex and the clinical implication can be counter intuitive. As such, Mundy-Bosse *et al.* found that increased numbers of highly functioning NK cells [defined by increased expression of perforin, granzyme B, and interferon (IFN)-γ] are associated with a worse prognosis. Overall, CD8 and NK cells can play important roles in the anti-tumor cytotoxic response to CTCL but higher NK cell activity may not correlate with better prognosis (9).

Immune evasion mechanisms in CTCL

Previous work has established that CTCL tumor cells, similar to other cancer cells, evade immune surveillance (10). Defects in components of the cellular immune system and reduced T-helper type 1 (TH1) activity are observed in MF/SS. Supporting a dampened TH1 phenotype is the reduced production of the pro-inflammatory cytokines IFN-α, IFN-γ, and interleukin (IL)-12 (11-13). In turn, an increased TH2 activity with elevated TH2 cytokines, IL-4, IL-5, and IL-10, which are known inhibitors of TH1-type cytokine production, has been demonstrated in SS/MF (14-16). A TH2 dominant immune environment reduces the TH1 driven anti-tumor CD8 cytotoxic response. Moreover, in a TH2 dominant environment, decreased numbers of dendritic cells and their products IL-12 and IFN-α occurs in MF/SS (17). All these changes contribute to the immune evasive conditions in CTCL.

Another hallmark of an immune evasive tumor microenvironment is the presence of hyporeactive or exhausted T cells (18). Expression of inhibitory molecules such as programmed death receptor-1 (PD-1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) is a feature of exhausted T cells. Signaling through these inhibitory molecules can be blocked with the use of checkpoint inhibitors in cancer treatment (19). In CTCL, increased expressions of PD-1, PD-1 ligand, and CTLA-4 have been demonstrated in lesional skin of MF patients (20). However, since inhibitory markers may be expressed on both malignant CD4 and cytotoxic CD8 T cells, it becomes difficult to determine how they may influence the anti-tumor response (21,22). We will discuss this paradigm further as we examine the use of checkpoint inhibitors in CTCL. Finally, regulatory T cells (Treg) play a role in dampening the immune response and upon infiltration in tumors, can contribute to immune evasion in malignancies (23). However, as in the case of circulating NK cells, broad generalizations about the role of specific immune effector cells in MF/SS should be avoided, as an increased number of Tregs in cutaneous lesions from patients with MF has been associated with improved survival (24). In CTCL, an increased number of Tregs has been observed in early MF lesions, but both malignant and reactive T cells can display phenotypic attributes of Tregs—most commonly forkhead box P3 (FOXP3) expression—and, in late MF stages, increased number of Tregs can in fact be associated with immune evasion (25,26).

Given the significant perturbations of the systemic and localized immune response in patients with CTCL, manipulation of the anti-tumor immune response via immunotherapy is an attractive treatment strategy in CTCL. Below we discuss the various existing and emerging immunotherapies used in CTCL.

Table 1 Monoclonal antibodies in MF/SS that are currently in use or in clinical development

Antibody	Target	Mechanism of action
Mogamulizumab[1]	CCR4 (C-C chemokine receptor type 4): CCR4 regulates T-cell skin homing by interacting with its ligands CCL17 and CCL22. CCR4 is highly expressed in tumor stage MF and SS (30)	ADCC and immunomodulation via reduction of Tregs (31,32)
IPH4102	KIR3DL2 (killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 2): KIR3DL2 is a co-inhibitory signal present on NK cells and on a subset of malignant T cells in MF/SS patients (33,34)	ADCC (33,34)
Alemtuzumab	CD52: CD52 is a glycosylated peptide antigen expressed on most malignant B and T cells but not on hematopoietic stem cells (35)	ADCC and CDC (35)
Brentuximab Vedotin[2]	CD30: CD30 is a transmembrane molecule of the tumor necrosis factor receptor family and is expressed in a subset of patients with MF (36)	Upon receptor binding, the antibody-drug conjugate (anti-CD30/MMAE) is internalized into lysosomes and MMAE release leads to cell cycle arrest and apoptosis (37,38)

[1], mogamulizumab was recently approved by the FDA for patients with stage IB–IV MF/SS who have received at least one prior systemic therapy; [2], brentuximab vedotin has been approved by the FDA in 2017 for patients with CD30-expressing MF who have received prior systemic therapy. MF, mycosis fungoides; SS, Sézary syndrome; ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; CCL17, C-C motif chemokine ligand 17; CCL22, C-C motif chemokine ligand 22; MMAE, monomethyl auristatin E.

Monoclonal antibodies (mAbs) that target neoplastic T-cells

Several mAbs targeting antigens expressed on neoplastic T-cells are currently in use for the treatment of CTCL. These antibodies bind to surface proteins expressed by the majority of, or major subsets, of malignant T cells and kill or deplete them via antibody-dependent cellular cytotoxicity (ADCC) (27), antibody-dependent cellular phagocytosis (ADCP), or complement-dependent cytotoxicity (CDC) (28,29).

Generally, the variable regions of these antibodies bind to their corresponding antigenic epitopes on malignant T cells. The Fc segment of the antibody in turn binds the Fc receptor on macrophages, NK cells, and other effector cells or activates complement. NK cells and macrophages are brought into proximity of tumor cells during this process and exert cytotoxic or phagocytic function against tumor cells. Since ADCC, ADCP, and CDC are killing mechanisms mediated by immune cells, they fit within the broader definition of immunotherapy. However, these destructive mechanisms are employed by all mAbs used in cancer treatment regardless of antibody specificity (29). The mAbs commonly used in the treatment of MF/SS and the surface markers they target on T-cells are listed in *Table 1* (30-36).

It should be noted that some of these mAbs are engineered to exert additional effector properties distinct from ADCC, ADCP, and CDC. For example, brentuximab vedotin is an antibody-drug conjugate (ADC) produced by conjugating the anti-CD30 mAb (cAC10) to the cytotoxic payload synthetic monomethyl auristatin E (MMAE) via a complex cathepsin-cleavable linker (37). Upon binding to CD30, brentuximab is internalized into lysosomes and MMAE release leads to cell cycle arrest and apoptosis (38). Other mAbs exert their antitumor effect via additional immune mediated alterations on the tumor microenvironment. For example, depletion of Treg cells by targeting C-C chemokine receptor type 4 (CCR4) with mogamulizumab has been proposed to induce a less immune evasive environment in CTCL (39).

IFN

Mechanism of action

IFN are natural cytokines with antiviral, cytostatic, and immunomodulatory activity that are used in the treatment of several forms of malignancies, including MF/SS. Three types of IFN (alpha, beta, and gamma) are known, with IFN-α and IFN-β grouped together as Type I and INF-γ constituting a distinct type II IFN (40). Both IFN-α and

IFN-γ have been used to treat CTCL with IFN-α being the most widely used type of IFN (41).

IFN-α treatment is believed to work by inducing a change in the immune evasive environment of MF/SS. Specifically, IFN-α administration shifts the TH2 dominant milieu towards a TH1 driven cytotoxic response. IFN-α inhibits IL-4 and IL-5 cytokine production (42,43). A shift to TH1 cytokines will further activate the anti-tumor response mediated by CD8 T-cells and NK cells (41).

IFN-γ is less commonly used to treat MF/SS, though in principle IFN-γ exerts similar effects as IFN-α, in shifting the TH1/TH2 paradigm in MF/SS. IFN-γ is a potent simulator of macrophages and dendritic cells and enhances the cytotoxicity mediated by CD8 T cells and activation of NK cells (44).

Monotherapy IFN-α

Bunn *et al.* initially studied the use of maximal dosage recombinant IFN-α (50×10^6 U/m^2 body surface area) in 20 patients with MF/SS stages II–IVB (45,46). In this prospective study, partial response (PR) (>50% decrease in measurable lesions for at least 4 weeks) was observed in 45% of patients and minor response (MR) (objective remission in some lesions but stable or progressive lesions in other areas) was seen in 25%. There were no patients with complete remission (CR) and 30% had no response (NR). Of the 45% of patients that experienced PR, 89% experienced objective extracutaneous improvements as well, including lymph node size reduction and decrease in circulating malignant cells. Overall, IFN-α demonstrated a 45% objective response rate (ORR), defined as any response in lesions for at least 4 weeks. However, IFN-α adverse effects, including an influenza like syndrome, fatigue, anorexia and depression, required dose reductions to at least 50% of the initial dose in all patients in the first three months of treatment. More importantly, after lowering the IFN-α dosage, ten patients experienced relapses and required dose re-escalations (45,46).

Several small and large scale studies that looked at the efficacy of single agent IFN-α at the maximum tolerated dose (MTD) in early and advanced stage MF/SS are summarized in *Table 2* (45-52). Combining the data from these studies, overall 183 patients received IFN-α. Of these, 37% achieved a PR and 24% a CR. Higher response rates were observed in patients with early stage disease, no prior systemic therapy, and treatment with higher doses of IFN-α. Overall, adverse events, including influenza like syndromes, leukopenia and reversible hepatotoxicity were significant. In a large, carefully characterized retrospective Australian cohort, 68 MF/SS patients treated with IFN-α had a longer time to next treatment (TTNT) when compared with other systemic therapies (TTNT of 8.7 months for IFN-α, 3.9 months for chemotherapy, and 4.5 months for histone deacetylase inhibitors) (53).

We conclude that while IFN-α is appropriately listed by the National Comprehensive Cancer Network (NCCN) guidelines as a standard therapy for CTCL, its safety profile limits its use in many patients, as evidenced by the frequency of dose reductions in single agent studies listed in *Table 2*. It should also be noted that the response criteria have changed dramatically since many of the earlier studies were conducted and published. Therefore, the CR, PR, and ORR rates reported here may not be directly comparable with those of newer studies.

Pegylated IFN-α

The addition of polyethylene glycol to standard IFN-α has led to the introduction of pegylated IFN-α to treatment modalities in MF/SS. This newer form has a lower rate of absorption and reduced clearance as compared with standard IFN-α (41).

In a small dose-escalation study by Schiller *et al.* evaluating pegylated IFN-α efficacy, 13 MF/SS patients were treated with 180, 270 or 360 μg/week for 12 weeks (52). Major response rates, defined as either a complete or partial remission, were observed in 50%, 83%, and 66% in the 180, 270 and 360 μg, respectively. The median response duration of 12 months was longer than the 5-month median response duration reported by Bunn's initial study with standard IFN-α dosing. More than a third (38%) of the patients in the Schiller study required dose reductions or dose holdings due to adverse events, with the highest number of patients requiring dose changes in the 270-μg cohort (n=4). Most commonly reported side effects included fatigue, leukopenia and hepatic toxicity, similar to the side effects observed in standard dose IFN-α studies.

Although Schiller's dose escalation study highlights pegylated IFN-α's more tolerable profile and suggests higher response rates, when compared with standard IFN-α, larger studies are necessary to confirm these results. A larger MF/SS patient population is necessary to evaluate comparisons between pegylated and standard IFN-α.

Table 2 Monotherapy IFN-α response in clinical studies

Study	Design and dosage	Subjects	Results	Adverse events
Bunn *et al.*, 1984 (45,46)	Prospective study	20 patients: 5 stage II; 2 stage III; 13 stage IV	0 (0%) CR	Influenza like syndrome (100%)
	50 MU weekly in 3 divided doses		9 (45%) PR	All patients needed 50% dose reduction
	IFN-α continued indefinitely for CR or PR, 3 months for SD or MR, or until progression in PD		5 (25%) MR	9 patients needed 90% dose reduction
			6 (30%) SD	
			Median response duration of 5 months	
Olsen *et al.*, 1989 (47)	Prospective study	22 patients: 4 stage IA; 3 stage IB; 5 stage IIA; 4 stage IIB; 4 stage III; 2 stage IVA	3 (13.6%) CR	Fatigue (100%)
	3 MU or 36 MU daily for 10 weeks		10 (45.5%) PR	Fever (86%)
			1 (4.5%) MR	Anorexia (55%)
			7 (31.8%) SD	Nausea (45%)
			1 (4.5%) PD	Other less common AEs included hair loss, depression, dry mouth, and dry eyes
			Higher rates of OR in 36 *vs.* 3 MU (79% *vs.* 37.5%, respectively)	
Kohn *et al.*, 1990 (48)	Prospective study	24 patients*: 17 stage IIB or higher; 14 with extra-cutaneous disease	1 (4%) CR	Influenza like syndrome (100%)
	10 MU on day 1 then 50 MU on days 2–5 every 3 weeks for 4 courses		6 (25%) PR	Reversible elevated liver enzymes (33%)
	If no CR or PD, doses increased to 20 MU on day 1 then 100 MU days 2–5 every 3 weeks		4 (17%) SD or PD	
			54% unclear	
			Median response duration of 8 months	
Vegna *et al.*, 1990 (49)	Prospective study	23 patients*: 12 with plaque lesions; 5 with generalized erythroderma; 4 with Sézary syndrome	8 (34.8%) CR	Influenza like syndrome (100%)
	Dose escalation from 3 MU to 18 MU daily for 12 weeks		9 (39.1%) PR	Toxicity (13.6%)
			2 (8.7%) SD	Leukopenia (26%)
			3 (13.0%) PD	
			1 (4.3%) died	
			Median time to CR was 5 months	
			100% CR/PR for stage IA	
			83% CR/PR for stage IB	
			80% CR/PR for stage IIA	
			57% Cr/PR for stage IVA	

Table 2 (*continued*)

Table 2 (*continued*)

Study	Design and dosage	Subjects	Results	Adverse events
Papa *et al.*, 1991 (50)	Prospective study	43 patients: 11 stage I; 9 stage II; 12 stage III: 5 stage IV; 6 Sézary syndrome; 28 newly diagnosed; 15 previously treated	11 (25.6%) CR	Influenza like syndrome most patients
	3 MU daily initially, escalated 3 MU every 3 days up to 18 MU daily		21 (48.8%) PR	Nausea, anorexia or vomiting (50%)
			6 (14.0%) SD	Somnolence (19%)
			4 (9.3%) PD	
			1 (2.3%) died	
			Greater response in early disease and previously untreated	
			Most relapsed within 23.5 months	
Jumbou *et al.*, 1999 (51)	Retrospective study	51 patients: 1 stage IA; 7 stage IB; 1 stage IIA; 30 stage IIB; 11 stage III; 1 stage IV; 35 previously untreated; 16 previously treated	21 (41.2%) CR	Treatment stopped in 39% due to AE**
	Induction therapy with 6 MU daily for 1 month		13 (25.5%) PR	
	Maintenance therapy with 6 MU or 3 MU 3 times a week		17 (33.3%) SD/PD	
			62.5% CR for stage I	
			45% CR for stage II	
			16.5% CR for stage III and IV	
			57% relapsed within average of 7.5 months	
Schiller *et al.*, 2017 (52)	Prospective study	13 patients: 7 stage IA; 6 stage IB	180 μg: 50% CR, 50% SD	180 μg: 75% had leukopenia or mild liver toxicity
	Pegylated IFN-α at 180, 270, and 360 μg once weekly for 12 weeks		270 μg: 67% CR, 17% PR, 17% SD	270 μg: 83% had AE—including leukopenia, thrombocytopenia, fatigue, insomnia, flu-like symptoms, moderate and severe liver toxicity, diarrhea
			360 μg: 54% CR, 15% PR, 31% SD	360 μg: all patients had AE—including anemia, leukopenia, thrombocytopenia, flu-like symptoms, mild liver toxicity
			Median duration of response of 12 months	

*, complete staging not available; **, specific information about adverse events is not provided. MU, million units; AE, adverse events; CR, complete remission; PR, partial remission; MR, mixed/minimal response; SD, stable disease; PD, progressive disease; OR, objective response.

Combination therapies with IFN-α

Combination therapy IFN-α has been introduced in an effort to augment standard IFN-α's response rate and duration of response, as well as to avoid dose-limiting toxicities. It is a treatment regimen that consists of administering low doses of standard IFN-α with already established treatment modalities for MF/SS patients, such as with psoralen and ultraviolet A (PUVA) radiation and with retinoids (54-57). Phase I and Phase II trials were initiated to investigate PUVA and IFN-α effectiveness for early and late stage MF/SS patients (56,57). Complete responses were obtained in 62% to 80% of the patients with a median duration of response greater than 13 months. Long-term prospective studies have established prolonged efficacy and tolerability with IFN-α and PUVA, with a CR of 84% (55). Studies on IFN-α and PUVA have catalyzed the development of IFN-α inclusion in other treatment regimens, including low dose bexarotene, a retinoid used for early stage MF (58).

IFN-α's augmenting properties expand its application in MF/SS. While its use in monotherapy was questionable due to dose limiting toxicities and short duration of responses, its efficacy as an augmenting agent prove more promising. Additional studies need to be conducted to examine its benefit in combination with the new emerging therapies.

IFN-γ

IFN-γ has been studied on a smaller scale in MF/SS. In one prospective study conducted by Kaplan and colleagues, 16 patients received IFN-γ. Thirty-one percent of patients had an objective PR with one of these patients having previously relapsed with IFN-α treatment (59). and no CR were observed. A subsequent small dose-escalating prospective study in 2004 showed was conducted for IFN-γ in CTCL (60). From five total MF/SS patients, one showed CR and others demonstrated PR. Additional studies on a larger scale are needed to establish a comparison between IFN-α and IFN-γ effect on MF/SS patients.

IL-12

Mechanism of action

IL-12 is a TH1 promoting cytokine, predominantly expressed by monocytes, that is a potent inducer of IFN-γ. IL-12 enhances NK cell activity and cytotoxic T cell responses in CTCL (61). As discussed before, a TH2 dominant cytokine milieu and reduced production of TH1-promoting cytokines such as IFN-γ and IL-12 are hallmarks of immune evasion in MF/SS (11,62). Preclinical studies demonstrated augmented cell lysis and tumor cell cytotoxicity after culturing cells from SS patients with IL-12, supporting this cytokine's role in anti-tumor immune function (61). Therefore, therapeutic IL-12 administration has been proposed and clinically used in MF/SS to shift the cytokine balance towards a TH1-dominant microenvironment, more favorable to anti-tumor response.

Clinical studies

A small scale (N=10) phase I trial using 50 to 300 ng/kg IL-12 for MF/SS, stages T1 to T4, was initiated to estimate IL-12 anti-tumor activity *in vivo* (63). Results showed improvement in the skin surface area affected by the disease, with 40% of plaque stage patients reaching CR and 40% attaining PR within 7–8 weeks. Conclusions about the effect of IL-12 in patients with SS could not be drawn due to the fact that 2 of the 3 SS patients withdrew from treatment. The one remaining patient experienced a PR at week 13. Two tumor stage patients were included in the study and received intralesional IL-12 treatments. While they both experienced resolution of the tumors injected with escalating doses of IL-12, new lesions continued to develop elsewhere. Overall, 20% of the patients showed CR, 20% showed PR, and remaining patients demonstrated NR, MR or local response. Biopsies and subsequent immunohistological analysis of patients with CR or PR showed a shift towards a TH1 environment post-treatment. Most adverse events experienced by the patients were mild and of short duration and included fatigue, headache and myalgias.

Although this study was too small to reliably assess efficacy, the biopsy results showing an increase in CD8 T cells suggest that IL-12 supplementation may play a role in augmenting the immune system's anti-tumor effects. An ongoing phase II trial (NCT02542124) examining the effects of IL-12 with total skin electron beam therapy (TSEBT), a highly effective therapy option for MF, is enrolling patients (64). Early results indicate that of five enrolled patients, one has achieved CR and two achieved PR. Continuation of the study with a larger patient enrollment is necessary to determine correlation with disease stage and show comparisons between TSEBT with IL-12 and TSEBT monotherapy. IL-12's clinical use for patients remains limited as it has not yet been approved for

MF/SS and its efficacy is being evaluated in clinical trials.

Extracorporeal photochemotherapy (ECP)

Mechanism of action

ECP is a therapeutic modality by which a patient's blood is drawn and centrifuged to separate the white blood cells (WBC) from the red blood cells and plasma. Methoxsalen (8-methoxypsoralen; 8-MOP) is added to the WBCs which are then exposed to UVA, leading to photoactivation of methoxsalen and formation of DNA adducts. Treated and untreated blood components are then reinfused to the patient (65). Photoactivated methoxsalen enters the malignant leukocytes and intercalates with DNA strands to induce apoptosis (66). In addition, ECP is proposed to possess immunomodulatory effects that have been referred to as "transimmunization" (67). Briefly, ECP leads to activation of monocytes and their differentiation into dendritic cells. Upon reinfusion, dendritic cells phagocytose apoptotic lymphocytes and present antigen peptides. Furthermore, an immune response shifting the TH1/TH2 environment has been described (67). However, the immunomodulatory effect of ECP can be complex due to its stimulatory effect on Treg differentiation and anti-inflammatory cytokine production (68).

Clinical studies

The efficacy of ECP in CTCL was first shown by Edelson *et al.*, with encouraging results in advanced stage MF/SS (69). Administering the therapy on two consecutive days every 4 weeks resulted in a 73% response rate in patients with resistant MF/SS with an average 64% improvement of cutaneous involvement. Moreover, 83% of erythrodermic patients experienced improvement of erythroderma. Further studies have demonstrated beneficial responses in MF/SS patients, either with ECP monotherapy or in combination with other treatment modalities such as IFN-α (70-76). Zic *et al.* compiled data from large series of over 400 CTCL patients of all stages treated with ECP and calculated an ORR of 55.7% and a 17.6% CR rate (65). In SS patients, peripheral blood flow cytometry showed clearance of detectable circulating Sézary cells and elimination of the malignant clones (74).

ECP gained United States Food and Drug Administration (FDA) approval in 1988. CTCL recommendation guidelines suggest ECP use for SS, erythrodermic MF and late stage MF (IIB to IV) that are refractory to other treatments (77). Its use in early-stage MF remains controversial. Additionally, randomized controlled trials comparing ECP efficacy with other established treatments for MF/SS have not yet been reported.

Toll-like receptor agonism

Mechanism of action

Toll like receptors (TLR) are primarily expressed on dendritic cells and macrophages and function as part of the innate immune system to recognize pathogen-associated molecular patterns (PAMPs) during infections and stress (78). Once bound to ligand, they stimulate antigen presentation, increase cell proliferation, and upregulate stimulatory molecule expression. Together, these functions enhance T cell activation and augment cell cytotoxicity against inflammation and tumors (79). Several TLRs are targeted in MF/SS, including TLR7 and TLR8 which bind viral RNA particles and TLR9 that binds bacterial and viral DNAs.

Imiquimod mechanism of action

In humans, TLR7 is solely expressed on a subset of dendritic cells called plasmacytoid dendritic cells (pDCs) (80). Targeting TLR7 with a synthetic ligand, imiquimod, induces production of pro-inflammatory cytokines by pDCs. Specifically, increased production of IFN-α by pDCs results in an increase in TH1 response and a shift towards an anti-tumor immune response.

Imiquimod clinical studies

Although evidence from large clinical studies is lacking, several case reports and case series demonstrate efficacy for imiquimod in treatment of MF/SS, findings summarized in *Table 3* (81-89). Results compiled from all studies show 24 treated MF patients, predominantly early stage, with 71% achieving CR and 17% having stable disease. The most common adverse events were skin irritation that self-resolved. In patients with CRs, there was a higher chance of developing severe skin reactions, such as ulcers or erosions that required dose reductions or even temporarily withholding treatment. While these results are promising, imiquimod is not currently approved for use in MF/SS. Larger trials are needed to assess the efficacy of imiquimod

Table 3 Topical 5% imiquimod response in clinical studies

Study	Design and subjects	Results	Adverse events
Suchin *et al.*, 2002 (81)	1 patient, stage IA: ❖ Treatment area compared with placebo treated area; ❖ Received treatment for 4 months	100% resolution of treated areas 100% histologically confirmed clearance Placebo lesions unchanged	Vesiculation, erosion, and xerosis requiring temporary cessation
Dummer *et al.*, 2003 (82)	1 patient with PUVA resistant MF: ❖ Received treatment for 2 weeks on face; ❖ Continued PUVA on extremities	100% resolution of treated facial lesions	Ulceration 10 days after therapy
Chong *et al.*, 2004 (83)	4 patients, stage IB: ❖ Treatment area compared with distant control area; ❖ Received treatments for 16 weeks	8.9% decrease in surface area of treated lesions 39.9% increase in surface area of control lesions	Mild lesional irritation in all patients
Deeths *et al.*, 2005 (84)	6 patients, stage IA to IIB: ❖ Received treatment for 12 weeks on up to 5 lesions; ❖ One index lesion was selected for pre and post treatment biopsy	50% histologically confirmed clearance of treated areas	Skin irritation in 4 patients (greater in those with histological clearance) Erosions/ulcerations in 2 patients
Chiam *et al.*, 2007 (85)	1 patient, stage IA: ❖ Received treatment on a single lesion every 2 days for 4.5 months	100% resolution of treated plaque	Pain during first week of treatment Skin erosion during 4th week requiring temporary cessation
Coors *et al.*, 2006 (86)	8 patients: ❖ 4 MF; ❖ 1 CD30+ anaplastic large cell lymphoma; ❖ 3 primary cutaneous B-cell lymphomas	50% resolution of treated areas in MF patients	Irritation, erythema and pruritus in 2 patients
Martínez-González *et al.*, 2008 (87)	4 patients, stages IA to IIB: ❖ 3 received imiquimod monotherapy; ❖ 1 received imiquimod and systemic IFN-α	100% resolution of treated areas 75% histologically confirmed clearance 25% partial histological clearance Most rapid clearance in combination treatment	Local irritation in some patients
Gordon *et al.*, 2015 (88)	2 patients, stages IB and IIB: ❖ Patient 1: stage IB treated twice weekly; ❖ Patient 2: stage IIB tumor MF treated 5 times weekly	Patient 1: resolution of treated lesions after 6 months Patient 2: resolution of tumor after 2 months Both patients developed new lesions in uninvolved areas	Erythema and Inflammatory response at site of application both patients
Lewis *et al.*, 2017 (89)	2 patients, stage IIB tumor MF both resistant to oral bexarotene 1 received imiquimod monotherapy 1 received imiquimod and oral bexarotene	100% resolution of treated tumors	Significant irritation and Influenza like syndrome in patient receiving imiquimod monotherapy

PUVA, psoralen and ultraviolet A; MF, mycosis fungoides.

in MF/SS.

Resiquimod mechanism of action

Similar to imiquimod, resiquimod belongs to the imidazoquinolone family. Unlike imiquimod, however, resiquimod modifies the immune response by binding to both TLR7 and TLR8. Although both receptors are structurally similar, they differ in their signaling and therefore, lead to the release of different cytokines.

Gorden and colleagues studied the effect of cytokine release when TLR7 and TLR7/8 were stimulated with their respective agonists (90). TLR7 induction led to a 5 to 10 times greater release of IFN-α whereas TLR7/8 stimulation led to an additional ten times greater production of TNF-α and IL-12. As discussed above, TLR7 engagement by its ligands primarily activates pDCs, causing the predominant IFN-α release associated with imiquimod therapy. However, TLR7/8 agonist stimulates a wider subset of monocyte derived dendritic cells and promotes a wider range of cytokine production, including IFN-α, TNF-α and IL-12.

Although IFN-α, TNF-α and IL-12 all work to augment the immune response, they each function differently. We previously discussed IFN-α and IL-12 function in detail. Briefly, TNF-α is an acute phase reactant that promotes the inflammatory response and inhibits tumorigenesis (91).

Resiquimod clinical studies

Topical resiquimod is a potent TLR7 and TLR8 agonist that is currently being studied in MF/SS patients. A phase I trial, enrolling 12 patients with stages IA to IIA MF, demonstrated promising results for stimulation of the antitumor cytotoxic response and subsequent lesion improvement (92). Patients enrolled were predominantly of early-stage MF with 83% having stage IB. CR was observed in 17% of the patients and PR was attained in 75% of patients. Furthermore, elevated dosage correlated with better response. Only minor adverse effects, such as local skin irritation, were reported by some patients. The trial demonstrated the clearance of untreated lesions as well as treated lesions, a response that had not yet been reported with other topical therapies.

Resiquimod treatment led to either reduction of the monoclonal T cell clone in skin biopsies (90%) or complete elimination of the clone (30%). An expansion of TNF-α and IFN-γ, cytokines mediating the CD8 and NK cell cytotoxic response were observed in lesional skin and correlated positively with treatment response. Overall, these findings provide evidence that resiquimod induction of TLR7 and TLR8 activity augments adaptive immune function.

Although only a small cohort of patients with predominantly early-stage MF were included in the phase I trial of resiquimod, the results show encouraging CR and PR rates. Additionally, this topical medication possibly induces a systemic response and improvement in even untreated lesions. A larger phase II trial is currently ongoing to assess the duration and efficacy of this systemic response (93).

TLR9 agonist mechanism of action

TLR9 is an intracellular receptor expressed on numerous immune cells and is activated by unmethylated CpG sequences found in bacterial or viral DNA. Ligand binding to TLR9 induces pro-inflammatory cytokine production such as type I IFNs and IL-12 (94).

TLR9 agonist clinical studies

In a phase 1/2 study by Kim *et al.* 15 MF patients received *in situ* intratumoral vaccination with TLR9 agonist CpG oligodeoxynucleotides combined with localized radiation (95). The hypothesis was that local radiation rendered tumor antigens more available to pDCs, which were in turn primed by TLR9 agonism. The overall response rate was 35.7% with an average time to response of 7.9 weeks and median response duration of 7 weeks. While intratumoral vaccination with TLR9 ligand presents a potential new immunotherapy for MF, larger studies are lacking to comprehensively determine its efficacy.

PD-1 blockade

Mechanism of action

The PD-1 (CD279) is a 268 amino acids transmembrane receptor protein encoded by the *PDCD1* gene on chromosome 2q37.3, a member of the extended CD28/CTLA-4 family of T-cell co-regulators. PD-1 is expressed by activated T cells, B cells and myeloid cells and promotes immune tolerance by transducing immune-inhibitory signals (96). Under normal conditions, most circulating T cells do not express PD-1. However, T cells can be induced to express PD-1 upon activation. The inhibitory signals relayed through PD-1 oppose uncontrolled activation of primed T cells through inhibition of T-cell proliferation,

cytokine production, and cytolytic function (97). In chronic viral infections, primed cytotoxic T cells express high levels of PD-1 on their surface, become hyporeactive, and are rendered unable to exert antiviral effector functions (98). Similarly, hyporeactive or "exhausted" CD8 T cells within tumors express high levels of PD-1 on their surface and become inefficient in eliminating tumor cells (99).

The two primary ligands that interact with PD-1 are programmed death-ligand 1 (PD-L1, also known as B7-H1 and CD274) and programmed death-ligand 2 (PD-L2, also known as B7-DC and CD273). The PD-1 pathway, consisting of the inhibitory receptor PD-1 on T cells and its ligands on antigen-presenting cells or tumor cells is a major mechanism of tumor immune evasion (100). In solid tumors, malignant cells can escape immune surveillance by expressing PD-L1 and inducing immune-inhibitory effects on tumor infiltrating T cells that express PD-1. Use of PD-1 inhibitors to block this interaction promotes anti-tumor immune response and has produced outstanding clinical results in cancer treatment (99).

In T cell malignancies, however, targeting PD-1 is a more complex proposition as malignant T cells may also express PD-1. Theoretically, PD-1 blockade can remove the inhibitory activity of PD-1 signaling in malignant T cells. In fact, it has been shown in a mouse model of T-cell lymphoma that the activity of PD-1 enhances levels of the tumor suppressor PTEN and attenuates signaling by the kinases AKT and PKC in pre-malignant T cells. Thus, the inhibitory PD-1 immune checkpoint receptor may function as a tumor suppressor in T cell lymphomas (101).

Several groups investigated the expression of PD-1 and its ligands in MF and SS. Samimi *et al.* detected PD-1 expression on both malignant (CD4+, CD26–) and non-malignant (CD4+, CD26+) T cells collected from blood of SS patients (22). PD-1 expression was significantly higher on circulating CD4 T cells from SS patients compared with either MF or healthy patients. Kantekure and colleagues retrieved MF tissue specimens and examined PD-1 and PD-L1 in patch, plaque and tumor stages (102). While lymphocytes in early patch and plaque stages showed elevated PD-1 expression, PD-1 expression was observed less frequently in tumor stages. However, the reported data did not distinguish PD-1 expression on malignant versus non-malignant T cells. PD-L1 tissue expression was found on all stages and was found to be increasing as tumor progressed. Overall, previous reports show evidence of expression for both PD-1 and its ligands but little is known about the extent of PD-1 activity in malignant versus non-malignant T cells in MF/SS.

Clinical studies

PD-1 blockade may be achieved through the use of anti-PD-1 mAbs such as pembrolizumab and nivolumab. In a phase I study to determine the efficacy of nivolumab in refractory hematologic malignancies, 13 MF patients and two patients with SS were included in the total of 81 subjects (103). In the MF group, two patients experienced PR (15%) while 0 had CR and 9 had SD (69%). Only one of the two SS patients had SD while the other patient showed progression of disease. Commonly reported adverse events included fatigue, skin reactions (rash and pruritus), and pneumonitis, with most events being graded as mild or moderate.

A phase II trial examining pembrolizumab (MK3475) efficacy in refractory MF/SS was conducted via the Cancer Immunotherapy Trials Network (CITN) (104). Khodadoust and colleagues enrolled 24 patients with higher stages of MF/SS in this trial, with 96% being stage IIB or above. Results showed 1 CR, 8 PR (33%), and nine patients with SD (38%). Median duration of response was 32 weeks. The most commonly reported adverse event was a skin flare reaction, with six patients experiencing this event. More serious adverse events, including pneumonitis and diarrhea, were observed in only two patients. As a result of this study, pembrolizumab is now listed in the NCCN guidelines compendium as a treatment option for CTCL and appears to be an acceptable treatment option for MF/SS. Future studies are being conducted combining pembrolizumab and other immunotherapies including IFN-γ.

In summary, PD-1 inhibitors can play a role in the treatment of a subset of patients with MF/SS given the ORR of 38% in the recent phase II trial. However, future work is needed to identify the characteristics of responder versus non-responders and to determine how PD-1 blockade affects malignant versus non-malignant T cells in MF/SS.

CTLA-4 blockade

Mechanism of action

CTLA-4 is another member of the costimulatory family of molecules for T cells and a homolog of CD28 (105). CTLA-4 is expressed on activated T cells and binds to its ligand B7 with much higher binding affinity compared to CD28. While binding of CD28 to B7 produces a stimulatory

signal in T cells, the competitive binding of CTLA-4 to B7 produces inhibitory signals that counteract the stimulatory signals from CD28:B7 binding (106). Blockade of CTLA-4 inhibitory signals in T cells has emerged as an effective form of cancer immunotherapy to activate tumor reactive T cells.

Wong *et al.* observed an abnormal *in vitro* up-regulation of CTLA-4 in peripheral blood T cells isolated from patients with MF (107). This upregulation was mediated by the TH2 transcription factor GATA3, which was overexpressed by the neoplastic T-cells in MF/SS, suggests that CTLA-4 contributes to the immunosuppression in MF/SS (108).

Clinical studies

Ipilimumab, a CTLA-4 blocking antibody, is used as an effective form of immunotherapy in solid tumors such as melanoma. However, its efficacy in CTCL has yet to be determined. In a single case report, a 44-year-old male with MF and melanoma, exhibited a complete resolution of MF cutaneous lesions after treatment with ipilimumab for advanced melanoma (109).

CD47

Mechanism of action

CD47 is a glycoprotein expressed on many normal cells and binds to its ligand, signal regulatory protein alpha (SIRPα), present on macrophages, dendritic cells and monocytes to inhibit macrophage phagocytic function (110). Upregulation of CD47 contributes to tumor immune evasion by preventing tumor cell elimination (111).

Targeting this pathway has been a major focus of immunotherapy for cancer, including breast cancer, Hodgkin lymphoma and ovarian cancer (112,113). Furthermore, CD47 blockade combined with rituximab has shown promising results for non-Hodgkin lymphoma in a phase 1b study (114). Its application in MF/SS has only recently been investigated

Clinical studies

TTI-62 is a CD47 antagonist that is currently in a phase I trial for MF/SS patients. Preliminary results from this trial show enrollment of 10 MF/SS patients (115). Lesion improvement was assessed using a composite assessment of index lesion severity (CAILS). Rapid reduction of CAILS and lesion improvement was observed in 90% of the patients. More importantly, in patients with circulating Sézary cells, all patients experienced reduction in circulating cell number after only one tumor injection. No toxicities required dose adjustments were reported.

Despite its use in other hematologic and solid cancers and its preliminary success in MF/SS, the specific mechanisms of CD47 blockade remain unclear. Future preclinical studies are essential to better understand this mechanism and its efficacy in MF/SS clinical settings.

Discussion

Recent breakthrough information about how malignant T cells in MF/SS evade the immune system has led to the development of therapies that aim at counteracting these mechanisms. Specifically, immunotherapies that enhance the immune system's anti-tumor responses are increasingly used in MF/SS. Studies and clinical trials have reported different success rates depending on the mechanism leading to the enhancement of CD8 T cell, macrophage, and NK cell function. While numerous studies have been conducted with older therapies, such as IFN-α and ECP, the evidence for clinical benefit of the newer therapies is starting to be gathered and looks very promising.

This review has highlighted the complex role of the immune system in controlling tumor cell growth in CTCL and the numerous pathways that are exploited by malignant cells to evade the anti-tumor immune response. We also survey the clinical benefits that have already been obtained with the introduction of new immunotherapies and highlight the promise of newer treatment strategies focused on modulating immune responses in CTCL.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare

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