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REVIEW

Advances in Immunotherapy for the Treatment of Cutaneous T-Cell Lymphoma

Ari Pelcovits[1,2], Thomas A Ollila[1,2], Adam J Olszewski[1,2]

[1]Department of Medicine, Alpert Medical School of Brown University, Providence, RI, USA; [2]Division of Hematology-Oncology, Rhode Island Hospital, Providence, RI, USA

Correspondence: Adam J Olszewski, Department of Medicine, Alpert Medical School of Brown University, Rhode Island Hospital, George Building, Ste 310, 593 Eddy St, Providence, RI, 02903, USA, Tel +1-401-444-2269, Fax +1-401-444-4184, Email adam_olszewski@brown.edu

Abstract: Cutaneous T-Cell Lymphoma (CTCL) is a heterogenous disease that consists of distinct clinicopathologic entities and presentations requiring a unique and expert approach to management. The most common subtype is mycosis fungoides, in which local disease has an excellent prognosis and is often managed with topical therapy alone. More extensive cutaneous involvement as well as involvement of lymph nodes and the peripheral blood (Sezary syndrome) require systemic therapies. Recent years have brought an expansion of therapeutic options, specifically with immune-based approaches that were developed using the knowledge gained regarding the biology and molecular pathology of CTCL. Previous systemic therapies such as retinoids, histone deacetylase inhibitors, and chemotherapeutic agents come with significant toxicity and only short-term response. Newer agents such as mogamulizumab and brentuximab vedotin use a targeted immune-based approach leading to longer periods of response with less systemic toxicity. While still in its infancy, the use of immune checkpoint inhibitors such as nivolumab and pembrolizumab appears promising, and while their current clinical application is limited, early data suggest possible future areas for research of immune manipulation to treat CTCL. Herein, we review these novel immune-based treatment strategies, their superiority over prior systemic options, and the ongoing need for further research and clinical trial enrollment.

Keywords: cutaneous T-cell lymphoma, Sézary syndrome, immunotherapy, brentuximab vedotin

Introduction

Cutaneous T-cell lymphoma (CTCL) is a malignancy of clonally expanded T-cells that infiltrate the skin.[1] The International Consensus Classification (ICC) of Mature Lymphoid Neoplasms and the 5th edition of the World Health Organization Classification of Haematolymphoid Tumours identify nine different clinicopathologic entities under the category of CTCL.[2,3] The most common subtype is mycosis fungoides (MF), which has excellent survival rates in early stages and is usually treated with topical therapy. However, outcomes worsen with more extensive skin involvement, and when the lymphoma spreads beyond the skin, the 5-year survival rate drops to less than 20%.[4] Sézary syndrome (SS) is a rare but aggressive form of CTCL characterized by erythroderma and blood involvement by malignant T-cells.[1] In recent decades, there has been significant progress in understanding the biology and molecular pathology of CTCL, particularly the expression of molecules associated with cell trafficking, immune activation, and exhaustion.[5,6] As current cytotoxic and cytostatic therapies for CTCL have limited efficacy and lack curative potential, there is growing interest in using immunotherapy for the treatment of advanced CTCL.[7–9]

CTCL (MF and SS) is staged using the TNMB (tumor, node, metastasis, blood) system, and responses to treatment can be described as global or specific to the T, N, or B compartments.[10] The T stage is defined by the type of visible lesions (patches, plaques, or tumors) and the amount of body surface area involved, with T4 disease indicating erythema that covers at least 80% of the body surface area. The B (blood) classification distinguishes low blood burden designated as B0 (<250/μL circulating atypical [Sézary] cells with an aberrant phenotype, most commonly CD4+CD7− or CD4+CD26−), B2 (defined as ≥1000/μL circulating Sézary cells), and B1 (cases not falling into either category). Treatment of localized disease is focused initially on skin-directed therapy with the use of topical agents, phototherapy, or radiation therapy.[11] Systemic treatment is reserved for more diffuse cutaneous spread, resistant disease, or extracutaneous involvement.[11] Systemic treatment options include retinoids, interferon

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alpha, histone deacetylase inhibitors, and chemotherapeutic agents, which usually result in short-lived responses and are associated with significant toxicity.[12] These agents, as well as the use of bone marrow transplantation (BMT), were extensively reviewed elsewhere.[6,9,13]

This paper reviews the immune-based treatments for CTCL (mainly monoclonal antibodies and antibody-drug conjugates) that are either currently available or under investigation. The immunopathogenesis of CTCL reflects the variety of relevant immune-targeting agents, and the differences in response to them in MF and SS (Figure 1). MF and SS likely evolve from distinct subsets of memory T-cells. SS is characterized by strong expression of CCR7 and L-selectin, which are both markers of central memory T-cells and play important roles in skin and lymph node homing.[14] In contrast, MF cells typically lack these markers and display an immunophenotype more consistent with skin resident memory T-cells, although some plasticity is possible in different compartments.[15] Both MF and SS T-cells show strong expression of CCR4, as well as the common T-cell antigens CD2, CD3, and CD4 (rarely CD8), with frequent aberrant loss of (one or more of) CD5, CD7, or CD26.[2,6] Monoclonal antibodies can produce an anti-lymphoma effect through several mechanisms, which include antibody-dependent cell cytotoxicity (ADCC, primarily involving NK cells), antibody-dependent cell phagocytosis (ADCP, primarily involving macrophages), complement-dependent cytotoxicity (CDC). These effects may occur on the tumor cells as well as on other immune cells in the lymphoma microenvironment, and the relative contribution of different mechanisms may vary among the antibodies.

Review

Denileukin Diftitox

Immune-targeted therapy has been used to treat advanced CTCL since the 1990s, starting with denileukin diftitox (DD), a recombinant protein that fuses the transmembrane domain protein (IL)-2 to the cytotoxic peptide of the diphtheria toxin.[16] DD exerts its action through direct cytocidal effect after internalization of the agent and intracellular release of the toxin. Clinical trials of DD in CTCL, which has a high expression of the IL-2 receptor, showed an overall response rate (ORR) of up to 49% with a duration of response (DOR) approaching 1 year. However, manufacturing difficulties led to the discontinuation of the agent in 2014.[17,18] An improved-purity form of DD (E7777) is currently being evaluated for potential reintroduction in CTCL and has shown an ORR of 36%, with a 9% complete response (CR) rate and a median DOR of 6 months.[19,20] The primary toxicity of diphtheria toxin-based therapies is capillary leak syndrome, which can cause edema, hypotension, and hypoalbuminemia, typically during the first 2 courses of therapy.[21]

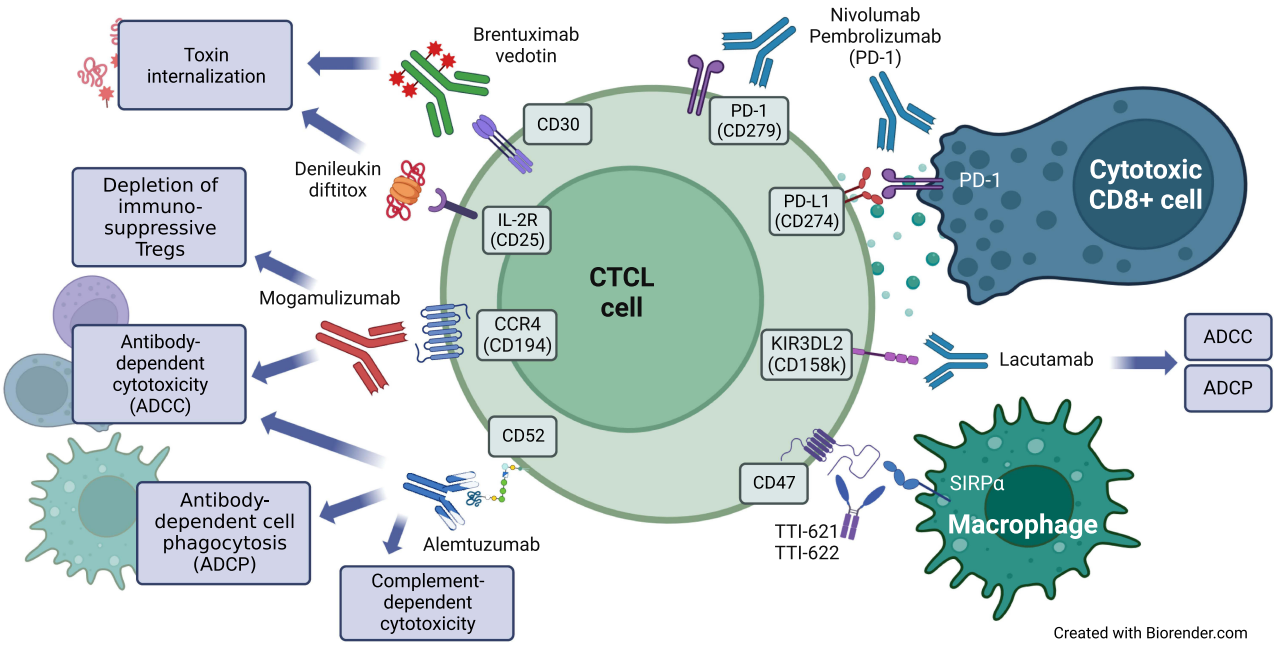

Figure 1 Cell surface targets and mechanisms of action of monoclonal antibodies in current use or under investigation in CTCL. Created with BioRender.com.

Alemtuzumab

Alemtuzumab, an anti-CD52 antibody, was initially developed to treat chronic lymphocytic leukemia, but it was later found to benefit patients with multiple sclerosis.[22] CD52 is expressed on mature B- and T-cells, with particularly high levels on malignant T-cells.[23] Alemtuzumab induces anti-lymphoma ADCC, but it unfortunately also effectively depletes effector T-cells. However, alemtuzumab may also exert direct cell-killing action via CDC.[24,25] In a Phase 2 trial of 52 patients with mycosis fungoides (MF) or Sézary syndrome (SS) (stage ≥2) who had received ≥1 prior line of systemic therapy, alemtuzumab demonstrated an overall response rate (ORR) of 55%, with a complete response (CR) rate of 32% and median duration of response (DOR) of 12 months.[23] Alemtuzumab cleared tumor cells from the blood in 6 out of 7 patients (86%), and the ORR in the skin was 56%. However, severe infections occurred in 50% of patients during treatment (2 of which were fatal), and 4 (18%) patients experienced reactivation of cytomegalovirus (CMV) infection. Furthermore, severe grade 4 neutropenia occurred in 18% of patients. Subsequent series of studies showed that the ORR in MF was less impressive (25%), although 15% of patients with SS maintained a CR for >2 years.[26]

Alternative administration schedules for alemtuzumab were investigated to mitigate the resulting immunosuppression. In a single-center study, 14 patients with SS (both previously treated and newly diagnosed) were treated with a reduced dose and slower dose escalation of subcutaneous alemtuzumab, along with strict hematologic parameters for holding therapy.[27] The ORR was 86%, with a CR rate of 21% and median time to treatment failure of 12 months. Four patients experienced infectious complications (29%), with one death, all within the group receiving the maximum dose of alemtuzumab (15mg compared with 30mg in the prior studies).

No phase 3 randomized trials of alemtuzumab have been conducted in CTCL. Alemtuzumab is listed as an alternative treatment option in the National Comprehensive Center Network (NCCN) guidelines, which note the improved response in SS compared with MF and reduced infectious complications with the lower and subcutaneous dosing.[11] However, alemtuzumab is currently only available for use in CTCL through the manufacturer's compassionate use program. In our practice, we limit its use to patients with refractory SS, often as a bridge to allogeneic bone marrow transplantation. It is important to monitor patients frequently for cytopenias and CMV reactivation (using polymerase chain reaction [PCR]) and to provide early therapy for viremia to maintain safety.

Mogamulizumab

T-cell migration and homing to the skin, which is a critical pathophysiological mechanism in CTCL, is regulated by a range of chemokines and cell surface receptors. CC chemokine receptor 4 (CCR4) is a receptor that is frequently expressed on CTCL cells and plays a role in T-cell migration.[14,28,29] Mogamulizumab, a defucosylated humanized IgG1κ anti-CCR4 monoclonal antibody, acts primarily through ADCC, but also leads to changes in the tumor microenvironment by selectively depleting tumor-residing Treg cells.[30] It has been approved for the treatment of patients with relapsed or refractory CTCL.[31] In a Phase 1/2 study of 41 patients with MF or SS, who had received at least one line of systemic therapy, the ORR to mogamulizumab (administered intravenously at 1.0 mg/kg weekly for 4 weeks and then every 2 weeks until disease progression) was 37%, with 47% ORR in SS.[32] Three patients had a CR to treatment, and the median progression-free survival (PFS) was 11.4 months.

These promising results led to the phase 3 MAVORIC study of mogamulizumab in 372 patients with MF or SS who had progressed after at least one line of prior systemic therapy.[33] Patients were randomized to receive either mogamulizumab or vorinostat (a histone deacetylase inhibitor), with a primary endpoint of PFS. CCR4 expression was not mandatory, and in an exploratory analysis, 97% of patients had CCR4 expression in the skin with no difference in response based on expression level.[33] Mogamulizumab resulted in a significantly improved PFS of 7.7 months compared to 3.1 months in the vorinostat arm. In a prespecified subgroup analysis, treatment favored mogamulizumab in stage III/IV disease but not in stage IB/II. Mogamulizumab also showed a larger advantage in SS than in MF. ORR was 28% versus 5% with vorinostat, with a median DOR of 14.1 and 9.1 months, respectively. Responses to mogamulizumab were higher in the blood compartment (68%) than in the skin (42%) or nodes (17%). The most common adverse effects of mogamulizumab were largely grade 1 and included infusion-related reactions (32%), drug rash (20%), diarrhea (23%), and fatigue (22%). Subsequent studies showed that CTCL progression on mogamulizumab often occurs in the setting of loss of CCR4 expression by the tumor cells.[34,35]

Based on the observed durable responses and low toxicity, mogamulizumab is designated as the preferred NCCN option for patients with SS.[11] However, several clinical aspects of mogamulizumab use warrant attention. The drug can cause infusion reactions as well as drug-related rash, which may rarely be severe. Hyperglycemia is noted in about 50% of patients with rare (4%) grade 3/4 glucose elevations. Furthermore, fatal graft versus host disease (GVHD) was observed in some patients with adult T-cell lymphoma/leukemia (ATLL) who underwent allogeneic BMT soon after mogamulizumab therapy, likely due to depletion of CCR4+ T-regs.[36] Although only one out of eight patients with MF/SS undergoing allogeneic BMT developed severe GVHD after mogamulizumab in one case series, maintaining the recommended minimum 50-day interval between mogamulizumab and an allogeneic BMT is prudent.[37] Finally, patients with large cell transformation of MF/SS were excluded from the pivotal trials, and the efficacy of mogamulizumab in this setting is unknown.

Brentuximab Vedotin

Brentuximab vedotin (BV) is an antibody–drug conjugate that targets CD30 and is linked to a microtubule toxin called monomethyl auristatin E. BV has been approved for the treatment of several malignancies that are characterized by CD30 expression, including Hodgkin lymphoma, anaplastic large cell lymphoma, and CD30+ peripheral T-cell lymphoma.[38–41] Additionally, a significant subset of CTCL cells express CD30, which is a hallmark of primary cutaneous anaplastic large cell lymphoma (pcALCL).[2,3,42]

CD30 targeted therapy's effectiveness in CTCL was first demonstrated in a phase 2 study of a naked anti-CD30 antibody SGN-30, with an ORR of 70%.[43] BV was subsequently tested in two phase 2 trials for relapsed/refractory CD30+ cutaneous lymphomas.[44,45] The first trial enrolled 48 patients with CD30+ CTCL after ≥1 prior systemic therapy, showing an ORR of 73% and CR rate of 35%.[44] Responses were assessed specifically in patients with MF according to the CD30 expression level, with no significant differences seen. ORR for patients with MF was 54% compared with 100% for typical CD30+ cutaneous lymphoproliferative disorders (lymphomatoid papulosis and pcALCL). The second multicenter trial was conducted strictly in patients with CD30+ MF/SS, also progressing after ≥1 prior line of systemic therapy.[45] The ORR was similar to the prior experience (70%), but a global CR was observed in only 1 subject. Patients were similarly grouped into categories of CD30 expression, and a statistically significant inferior response was noted among 6 patients with low (<10%) expression.

The ALCANZA trial was a randomized phase 3 trial of patients with CD30+ (defined as ≥10% expression) MF or pcALCL after ≥1 prior line of systemic therapy, comparing BV against physicians' choice of standard of care (oral methotrexate or bexarotene).[46] BV was administered intravenously at 1.8 mg/kg for up to 16 three-week courses; similarly, methotrexate or bexarotene were continued for up to 48 weeks. The primary endpoint was an objective response lasting at least 4 months (ORR4), which was attained by 56% of patients in the BV arm compared with 12% in the control arm. CR rates were 16% and 2%, respectively, median PFS was 16.7 and 3.5 months, respectively, and median DOR was 15.1 and 18.3 months, respectively. The toxicity of BV was similar to prior experience. Peripheral neuropathy was the most common adverse event occurring in 67% of patients, but only 9% experienced grade 3 neuropathy, and 82% reported improvement or resolution of symptoms. Nausea (36%), diarrhea (29%), and fatigue (29%) were also common, but low-grade in most cases. Serious adverse events occurred in 29% of patients treated with BV, and 24% of patients discontinued the drug due to toxicity.

Observational data confirm high responses to BV in both MF and SS. Among 67 CTCL patients from the Spanish Primary Cutaneous Lymphoma Registry, ORR was 63% in MF, 71% in SS, and 84% in other CD30+ lymphoproliferative disorders.[47] Similar ORR rates (69% and 62%, respectively) were reported in a retrospective analysis from nine European Organization for Research and Treatment of Cancer (EORTC) centers. The median duration of response (DOR) was 9 months, with higher ORR in the skin (72%) than in the lymph nodes (47%) or blood (40%).[48] However, a small single-institution series of 13 patients with relapsed/refractory SS reported lower response rates: 38% global, 38% in the skin, 63% in the blood, and 50% in the lymph nodes, with a median DOR of only 5.5 months.[49] Based on the summary of the evidence, BV is an excellent immunotherapy option for patients with either MF or SS expressing the CD30.

PD-1/PD-L1 Blockade

Immune checkpoint inhibitors, specifically PD-1-directed monoclonal antibodies like nivolumab and pembrolizumab, have been effective in treating various solid malignancies and hematologic cancers, including Hodgkin lymphoma and primary mediastinal B-cell lymphoma.[50,51] Their success is attributed to their ability to disrupt the inhibitory PD-1/PD-L1 interaction, which unleashes

the activity of cytotoxic tumor-infiltrating CD8+ T-cells.[52,53] However, using PD-1 inhibitors in T-cell lymphomas, such as CTCL, is challenging due to the fact that T-cell lymphoma cells may themselves express PD-1, which maintains an antiproliferative effect.[54,55] In some cases, checkpoint inhibition can trigger a massive and potentially fatal "hyperprogression" of a T-cell lymphoma, as observed in ATLL.[56] In CTCL, PD-1 expression is common in SS (89%) but less so in MF (13%).[57,58] *PDCD1*, the gene encoding PD-1, is deleted in 1/3 of SS cases and is mutated in cases with accelerated proliferation, suggesting a potential mechanism of escape from the negative PD-1-driven regulation as the disease progresses.[54,59] Despite increased proliferation of SS cells upon PD-1 blockade in pre-clinical models,[60] only one case of hyperprogression has been reported in the clinical setting, with worsening skin lesions, lymphocytosis, and upregulation of the activation marker CD69 on malignant T-cells.[61]

Clinical data on immune checkpoint inhibitors in CTCL are promising, leading to the inclusion of off-label pembrolizumab in the NCCN guidelines.[11] The initial evidence of efficacy came from a phase 1 trial of patients with various hematologic malignancies treated with nivolumab.[62] Out of 15 patients with CTCL included in this study, two (both MF) showed responses. A phase 2 trial of pembrolizumab enrolled 24 patients with CTCL who had received a median of four prior lines of systemic therapy.[63] The observed ORR was 38%, with 2 patients achieving a CR. Responses occurred in 56% of patients with MF and 27% of those with SS, and median DOR was not reached after median 58 weeks of follow-up. Thirty-eight percent of patients experienced an immune-related adverse event, but grade 4 or 5 toxicities were absent. Responders showed an expansion of CD8+ cytotoxic T-cells, suggesting that the efficacy of pembrolizumab is mediated by activation of anti-tumor immunity.[64] The increased proliferation of malignant T-cells was not observed in patients treated with pembrolizumab, although some may experience transient flares of erythroderma.[64]

Other PD-1 and PD-L1 inhibitors are under investigation for CTCL. Tislelizumab, a humanized anti-PD-1 monoclonal antibody, showed a promising ORR of 45% (with 9% CR rate) in 11 patients with CTCL enrolled in a phase 2 trial.[65] Other anti-PD-1 antibodies under investigation include durvalumab and sintilimab. PD-L1 is not overexpressed on CTCL cells compared to healthy controls[66] but becomes overexpressed in cases with large-cell transformation that acquire structural variants in *CD274* (the gene encoding PD-L1).[67] Initial data from the phase 2 trial of atezolizumab in relapsed/refractory MF/SS suggested a disappointing ORR of 15% with a median PFS of 3 months and 15% risk of sepsis (fatal in 7%).[68]

Novel Targets: KIR3DL2 and CD47

KIR3DL2 (CD158k) is a surface antigen expressed on CTCL cells (85% of SS) and is a member of the killer cell immunoglobulin-like receptor (KIR) class.[69,70] Its binding to MHC class I molecules inhibits cytotoxicity for NK cells and some CD8+ T-cells, but it is expressed on few normal immune cells.[71] Lacutamab (IP4102) is a humanized anti-KIR3DL2 monoclonal antibody currently in clinical development for CTCL therapy.[71,72] Lacutamab acts primarily through ADCC and ADCP, but it generally does not bind complement.[72] In a phase 1 trial, the agent showed no dose-limiting toxicities up to the recommended phase 2 dose of 750 mg. The most common adverse events were related to grade 1/2 peripheral edema (27%), fatigue (20%), fever, diarrhea, and arthralgia (16% each).[73] Preliminary results from the phase 2 trial indicate global confirmed ORR of 22%, including skin in 35% and blood in 38% in a relapsed/refractory SS after at least 2 lines of therapy including mogamulizumab.[74] The combination of lacutamab with PD-1 inhibitors may be worth investigating because decreased KIR3DL2 expression is associated with a higher chance of response to pembrolizumab.[64]

TTI-621 and TTI-622 (PF-07901801) are fusion proteins containing the CD47-binding domain of SIRPα and an Fc portion of the human IgG1 or IgG4 (respectively). CD47 is highly expressed on Sézary cells both in the blood and cutaneous compartments, where it can serve as a receptor for thrombospondin-1 (which stimulates Sézary cell migration and growth),[75] as well as a surface checkpoint inhibitor molecule that binds SIRPα on macrophages.[76] TTI-621 and TTI-622 act by blocking the immune checkpoint interaction between the CD47 on MF/SS tumor cells with SIRPα on macrophages, enabling the phagocytosis of the tumor cells.[77,78] In a phase 1 setting, responses to TTI-621 were recorded in 1 of 4 patients with SS and 5 of 19 with MF, for an ORR in CTCL of 21% (including one CR).[77] TTI-622/PF-07901801 has produced a response in 3 of 6 CTCL patients in a phase 1 trial, including 1 CR.[79] Toxicities of both agents were low-grade, reversible, and primarily hematologic (most frequently, thrombocytopenia). In contrast to other CD47-directed agents, TTI-621 and 622 were not associated with high rates of severe anemia. Preliminary data suggest that TTI-621 may also enhance the response to PD-1 inhibition in CTCL cell lines.[80]

Ongoing Investigations

Several ongoing trials (referred herein by their identifiers in the ClinicalTrials.gov database) are examining combinations of the immunotherapeutic agents reviewed above, as well as alternative targets. NCT05414500 is a phase 1 dose-escalation study evaluating the combination of BV and mogamulizumab in patients with previously treated CTCL, including those who were previously treated with BV. Although lenalidomide, an immunomodulatory agent, has limited activity as a single agent against CTCL, it is currently being evaluated in at least two trials as an augmentation to immunotherapy.[81] NCT03409432 is a phase 2 trial combining BV with lenalidomide in relapsed/refractory T-cell lymphomas, including CTCL. NCT03011814 is a phase 1/2 trial of lenalidomide and durvalumab in relapsed/refractory CTCL. The preliminary report of the phase 1 portion indicated promising activity with 9 out of 12 enrolled subjects responding.[82] Another phase 1 trial (NCT04652960) is investigating the combination of nivolumab with the phosphoinositide 3-kinase inhibitor duvelisib. Other potential targets for immunotherapy in CTCL under consideration include ICOS,[83] TIGIT,[35,84] CD70 (the ligand of CD27),[85] and CD38, which is also overexpressed on CTCL cells.[86] Zanolimumab, an anti-CD4 antibody, was investigated with preliminary success in a phase 2 trial, and a phase 3 trial was initiated, but the development of the drug was subsequently halted for business reasons.[87]

CAR T-cell therapy is an immunotherapy approach that has revolutionized the management of relapsed/refractory B-cell lymphomas, leukemias, and myeloma.[88] However, developing suitable CAR T-cell products against CTCL and other T-cell lymphomas is hampered by several issues, including the antigen overlap between malignant and infused T-cells, the potential for inadvertent transduction of harvested Sézary T-cells, fratricide, and complications of prolonged T-cell aplasia.[89] Allogeneic products or CAR NK-cells may help overcome some of these limitations (ability to generate autologous product from immunosuppressed donors, reinfusion of SS tumor cells, fratricide), but pose other challenges related to their persistence and the theoretical risk of GVHD.[90,91] Nevertheless, early clinical investigations are underway for CAR T-cells targeting CD4, CD7, CD37, CD70, CCR4 and other antigens (with suitable knockouts to prevent fratricide and GVHD) in various T-cell lymphomas.[92–95] For a more detailed information on this emerging field of research, including a comprehensive listing of targets and ongoing clinical trials, we refer the reader to recent specialized reviews.[89,96]

Conclusions: Our Current Approach and Future Directions

The currently available immunotherapy agents for CTCL include mogamulizumab, BV, and pembrolizumab (Table 1). While effective and tolerable, they are not approved for first-line treatment and require long-term intravenous administration with frequent visits. Standard first-line therapy options include bexarotene, oral methotrexate, or oral histone deacetylase inhibitors, which may be less burdensome to patients, but their efficacy becomes very limited in more

Table 1 Currently Available Immunotherapy Agents for CTCL

Drug	Level of Evidence	Diseases	Efficacy	Toxicity
Mogamulizumab	Phase 3[33]	MF, SS	• ORR 28%, • PFS 8 mos • DOR 14 mos • Improvement over HDAC in stage III/IV, SS	• Infusion reaction • Drug rash • Diarrhea • Fatigue
Brentuximab vedotin	Phase 3[46]	pcALCL, CD30+ MF*	• ORR 56% • PFS 17 mos • DOR 15 mos	• Neuropathy
Pembrolizumab	Phase 2[63]	MF, SS	• 38% • DOR not reached	• irAE
Alemtuzumab	Phase 2[23]	MF, SS	• ORR 55%, CR 32% • ORR in SS 86% • DOR 12 mos	• CMV reactivation • Severe infection

Note: *No difference noted in prespecified subgroups of CD30 expression, but post hoc analysis showed significantly less response in patients with <5% expression, and ALCANZA trial only enrolled patients with at least 10% CD30+ malignant or lymphoid infiltrative cells.

advanced MF or SS. Cytotoxic chemotherapy is rarely used in advanced CTCL, except as bridging disease control before consolidative BMT in cases with aggressive, large cell transformation.

Therefore, we usually institute immunotherapy as a second-line therapy, as the risk/benefit ratio becomes favorable. If CD30 expression (>5%) is detected and the patient does not have underlying neuropathy, BV is our preferred agent, although there is uncertainty about the minimal necessary cutoff of CD30 expression. For other patients, mogamulizumab is typically the most reasonable alternative, providing durable responses even in advanced SS (without large cell transformation). Pembrolizumab is an acceptable alternative, but vigilance is necessary regarding the risk of erythrodermic flare or hyperprogression. Alemtuzumab is limited by toxicity and availability, but it can be helpful for refractory SS patients with close surveillance for opportunistic infections. Allogeneic BMT, a form of radical immunotherapy, retains curative potential for select patients and should be considered during or after the first line of immunotherapy, given the high chance of further progression.

As none of the available agents provide a cure, we prioritize enrollment in clinical trials of novel approaches whenever possible. Combinations of immunotherapeutic antibodies have demonstrated safety in other malignancies, such as BV and PD-1 antibodies in Hodgkin lymphoma or mogamulizumab and PD-1 antibodies in solid tumors, and should be further investigated in CTCL.[97,98] Agents targeting KIR3DL2 and CD47 may potentiate checkpoint inhibitors, but further establishment as single agents is necessary. In the near future, CAR T-cell therapy may offer a potentially curative, immune effector cell-engaging approach.

Disclosure

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