The immunopathogenesis and immunotherapy of cutaneous T cell lymphoma: Current and future approaches

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Learning objectives
After completing this learning activity, participants should be able to employ each treatment based upon disease stage and type of CTCL and employ multimodality immunotherapy using the various discussed therapeutic agents in combinations based upon the stage and type of CTCL.

Disclosures
Editors
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

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In the past few decades, immunotherapy has emerged as an effective therapeutic option for patients with cutaneous T cell lymphoma (CTCL). CTCL is characterized by progressive impairment of multiple arms of the immune system. Immunotherapy targets these deficits to stimulate a more robust antitumor response, thereby both clearing the malignant T cells and repairing the immune dysfunction. By potentiating rather than suppressing the immune system, immunotherapy can result in longer treatment responses than alternatives such as chemotherapy. In recent years, advances in our understanding of the pathogenesis of CTCL have led to the development of several new agents with promising efficacy profiles. The second article in this continuing medical education series describes the current immunotherapeutic options for treatment of CTCL, with a focus on how they interact with the immune system and their treatment outcomes in case studies and clinical trials. We will discuss established CTCL immunotherapies, such as interferons, photopheresis, and retinoids; emerging therapies, such as interleukin-12 and Toll-like receptor agonists; and new approaches to targeting tumor antigens and checkpoint molecules, such as mogamulizumab, anti—programmed cell death protein 1, anti-CD47, and chimeric antigen receptor T cell therapy. We also describe the principles of multimodality immunotherapy and the use of total skin electron beam therapy in such regimens. (J Am Acad Dermatol 2021;84:597-604.)

Key words: CTCL; cutaneous T cell lymphoma; dermatologic oncology; drug response; immune deficiency; immunopathogenesis; immunotherapy; mycosis fungoides; Sézary syndrome.
ESTABLISHED THERAPIES

Interferon-alfa

Interferons (IFNs) are among the first immune-potentiating agents successfully used to treat cutaneous T cell lymphoma (CTCL). Both IFN-alfa (IFN-α) and IFN-gamma (IFN-γ) are cytokines produced as part of the innate immune response, and their multifold immunomodulatory effects have been harnessed to combat a variety of malignancies, including CTCL.

IFN-α, produced by plasmacytoid dendritic cells (DCs), targets several of the immune deficits present in CTCL, helping to bolster an antitumor response. Specifically, IFN-α has been found to stimulate CD8⁺ T cells and natural killer (NK) cells, thereby activating antitumor cytotoxicity (Table 1). Moreover, IFN-α may upregulate major histocompatibility complex class I expression on malignant lymphocytes. IFN-α can also blunt the excess T-helper 2 (Th2) production of interleukin-4 (IL-4) and IL-5 by malignant T cells, helping restore the host Th1/Th2 balance. While these effects have proven useful in inducing disease regression and control, the development of resistance may occur. Proposed mechanisms of resistance include the production of neutralizing antibodies, decreased expression of IFN receptors, and mutations and deletions of STAT1. Importantly, IFN-α should be used with care in patients with CD8⁺ CTCL, and not used at all for gamma/delta T cell lymphomas or for the initial phase of treating panniculitic T cell lymphomas, as these conditions are typically associated with cytotoxic T cells that release proinflammatory cytokines.

While there are few randomized controlled trials using IFN-α for CTCL, both retrospective and prospective studies have described impressive responses to this agent. Importantly, there are several forms of IFN-α: recombinant IFN-α2a and IFN-α2b, as well as pegylated IFN-α2a and IFN-α2b. Most studies have evaluated recombinant IFN-α, but both recombinant and pegylated IFN-α may be used to treat CTCL, and anecdotal reports suggest higher response rates with pegylated forms. One prospective analysis by Papa et al. observed that 80% of early stage patients and 70% of patients with Sézary syndrome (SS) responded to IFN-α. A trial by Olsen et al. similarly discovered that 59% of patients of all stages responded to the drug after 10 weeks of treatment. This same study found a dose-response curve indicating a possible advantage of higher dosage strategies when patients are resistant to lower doses. IFN-α has also demonstrated value in multimodality regimens. In particular, IFN-α has been shown to augment clinical response rates when added to psoralen plus ultraviolet A light phototherapy. Smaller scale studies also indicate possible efficacy of IFN-α when combined with oral retinoids, photopheresis, total skin electron beam therapy (TSEBT), and narrowband ultraviolet B light phototherapy.

IFN-α is generally tolerable at low doses, but various adverse effects may occur. Shortly after initiation of treatment, patients may develop flu-like symptoms that typically diminish and usually resolve within a few weeks. Potential chronic complications include fatigue, weight loss, depression, and impaired cognitive function. Myelosuppression may also occur, which usually does not require discontinuation if neutrophils remain above 1000 per µL. Less common adverse effects include hypothyroidism,
IFN-γ

IFN-γ, produced mainly by CD8⁺ T cells and NK cells, enhances cell-mediated cytotoxicity, antigen presentation, and TH1 immunity. IFN-γ, like IFN-α, activates CD8⁺ T cells and NK cells. Importantly, IFN-γ can prime and activate DCs and macrophages, thus pairing well with proapoptotic agents by enhancing processing of released tumor antigens. As the prototypical TH1 cytokine, IFN-γ can prime antigen-presenting cells, which are critical for the afferent response, and to stimulate NK and CD8⁺ T cells. Wysocka et al²² showed that subcutaneous granulocyte-macrophage colony-stimulating factor injections can increase the numbers of circulating DCs, which are characteristically diminished in SS.²³ In mice, studies have shown that administering an excessively large number of apoptotic cells may suppress DC function, further supporting the use of DC-potentiating cytokines with photopheresis.²⁴ Additional therapies that can be useful to pair with photopheresis include oral retinoids, psoralen plus ultraviolet A light phototherapy, and low-dose (12 Gy) total skin electron beam therapy.

Photopheresis is well-tolerated and few adverse effects have been reported.²⁴ Among erythrodermic patients, it is recommended that peripheral vascular access be obtained and that external Hickman catheters be avoided as there has been a high frequency of *Staphylococcus aureus* contamination.

Retinoids

Retinoids are another standard therapeutic option that at least partially target the immune dysregulation of CTCL. Retinoids act through retinoid X receptors (RXRs) and retinoic acid receptors (RARs). When bound, RXRs and RARs can form heterodimers with other nuclear receptors to act as transcription factors, resulting in multiple beneficial immunomodulatory effects.

Bexarotene is a synthetic rexinoid that selectively binds RXRs, and it has demonstrated usefulness and safety in all stages of CTCL. Though the full effects of bexarotene in CTCL have not been elucidated, it notably induces apoptosis of malignant T cells.²⁵ Moreover, bexarotene inhibits production of TH2 cytokines that are upregulated in CTCL.²⁶ Bexarotene also inhibits skin trafficking of malignant T cells by reducing C-C chemokine receptor type 4 (CCR4) expression and chemotaxis.²⁰,²⁷ Resistance has been noted in many patients, possibly through loss of RXR expression on malignant T cells.²⁸ Use of bexarotene in combination with other agents may decrease the frequency of resistance and optimize treatment outcomes. The most frequent side effects of bexarotene are hyperlipidemia and hypothalamic hypothyroidism, which occur in most patients.²⁹,³⁰ Thus, the monitoring of thyroid hormone replacement should be made by using the serum free T4 as serum levels of thyroid-stimulating hormone are depressed by bexarotene.

RAR retinoids, particularly isotretinoin, may provide added benefit in all stages of CTCL. There are several settings in which they are especially useful, including the treatment of advanced folliculotropic mycosis fungoides and suppression of new
squamous cell cancers among patients with this additional issue.\textsuperscript{31} In contrast, there is no evidence that bexarotene can slow squamous cell skin cancer growth.

**NEW AND EMERGING THERAPIES**

**IL-12**

IL-12 is a 70-kD heterodimeric protein produced by many cell types within the immune system. Notably, like IFN-\(\alpha\) and IFN-\(\gamma\), it is considered a product of the innate immune response, but it represents a critical link between innate and adaptive T cell immunity. Monocytes and, particularly, DCs, are the most significant producers of IL-12. This cytokine can potently activate NK cells and CD8\(^+\) T cells with the subsequent production of IFN-\(\gamma\). IFN-\(\gamma\) then enforces a T\(_{H1}\) immune response, which is critical for the development of a robust antitumor immune response.

Studies of immune dysregulation in CTCL found that the majority of patients in advanced stages of disease, particularly those with SS, exhibited profound defects in T\(_{H1}\) immunity associated with reduced numbers of circulating DCs and markedly diminished production of IFN-\(\gamma\) and IL-12.\textsuperscript{22,52} Because there is a bias toward T\(_{H2}\) immunity with increased production of IL-4, IL-13, and often IL-5, it was notable that IL-12 exhibited the ability to suppress T\(_{H2}\) cytokine production from circulating mononuclear cells in patients with SS.\textsuperscript{5,52} These observations served as the impetus for the initiation of several successful clinical trials with recombinant IL-12.\textsuperscript{33-36} IL-12 is presently not in clinical development for CTCL, and therefore details of the use of this potentially valuable and clinically effective cytokine are beyond the scope of this review.

**Toll-like receptor agonists**

IFN-\(\alpha\), IFN-\(\gamma\), and IL-12 are all products of innate immune activation and have each demonstrated significant clinical efficacy for CTCL. Therefore, another logical immunotherapeutic approach for CTCL is direct triggering of innate immunity via Toll-like receptor (TLR) agonists. Stimulation of TLR-7 or TLR-9 on plasmacytoid DCs results in the production of IFN-\(\alpha\), while activation of TLR-8 on myeloid DCs results in the release of IL-12, tumor necrosis factor–alfa and other immune potentiating cytokines, including IFN-\(\gamma\). It was hypothesized by Suchin et al\textsuperscript{57} nearly 20 years ago that the application to active CTCL skin lesions of imiquimod cream, a TLR-7 agonist, should prove beneficial through the induction of the local release of IFN-\(\alpha\). Indeed, the initial patient experienced a complete clinical response.\textsuperscript{57} Subsequent studies have demonstrated mixed results, although some series have produced high response rates. One series of 20 patients with early-stage disease who were treated with imiquimod had an overall response rate of 80%, and 45% had a complete response.\textsuperscript{30}

A confounding issue with imiquimod is low bioavailability. Persistent, long-term use typically produces greater efficacy. Furthermore, increasing the amount applied to a larger surface area can be quite helpful, although this is limited by the drug being dispensed in 0.25-g packages. Importantly, the simultaneous use of topical steroids at the same sites of application of imiquimod can eliminate the beneficial effects as the functions of DCs are inhibited by corticosteroids.

Because myeloid DCs, which express TLR-8 but not TLR-7, populate the skin in greater numbers than TLR-7–expressing plasmacytoid DCs, there is rationale for using a TLR-8 agonist.\textsuperscript{39} In that regard, a phase I trial of resiquimod gel, a TLR-7/8 agonist, for early-stage disease conducted by Rook et al\textsuperscript{39} resulted in high response rates among 12 treated patients. All but 1 patient experienced significant improvement in skin lesions. Two patients experienced long-term complete remission. Using high-throughput T cell receptor (TCR) sequencing analysis of skin DNA samples from serial skin biopsy specimens of treated lesions, the malignant T cell clone appeared to be eradicated from 4 of 10 patient samples and significantly reduced in another 5 patient samples. Moreover, a common finding during 8 weeks of topical therapy was intense infiltration of treated lesions with CD8\(^+\) T cells that were expressing granzyme and IFN-\(\gamma\). In addition, non-treated distant lesions quite commonly regressed, indicating that resiquimod has the potential for an abscopal effect.

Resiquimod also has the ability to activate circulating cells. Many patients treated in the phase I trial exhibited activation of both circulating DCs and NK cells. The ability to produce systemic immune activation with a topical agent that can induce the release of both IFN-\(\alpha\) and IL-12 as well as produce an abscopal effect is likely to be a valuable addition to the profile of immunotherapy drugs available for CTCL.

Limited trials of systemically administered TLR-agonists have also been undertaken for CTCL. Cytosine-guanine oligodeoxynucleotides, which bind to TLR-9 and thereby activate plasmacytoid DCs, were administered subcutaneously in increasing doses in a phase I trial for advanced refractory CTCL.\textsuperscript{40} A 32% response rate was observed. Considering that the maximal tolerated dose was not reached, these initial results appear to be promising.
Common side effects of imiquimod include skin irritation, inflammation, and itchiness, although one case report describes the development of flu-like symptoms. Resiquimod is similarly well-tolerated and has been found in clinical trials to generally cause mild adverse effects, such as skin irritation.

TARGETING OF TUMOR ANTIGENS AND CHECKPOINT MOLECULES

At present, the only unique tumor marker identified on Sézary cells appears to be the TCR of the malignant T cell characterized by a unique TCR gene rearrangement. Because these vary greatly from patient to patient, targeting the TCR is a highly complex approach. However, there are certain cell surface molecules that tend to be highly expressed on the malignant T cell population, including CCR4, programmed cell death protein 1 (PD-1), and CD47, which could provide for a common targeting approach.

Mogamulizumab

Mogamulizumab is an anti-CCR4 antibody that is approved by the US Food and Drug Administration for the treatment of relapsed or refractory CTCL. By targeting CCR4, which is overexpressed in the tumor cells of many patients with CTCL, mogamulizumab mediates elimination of malignant T cells by antibody-dependent cell-mediated cytotoxicity (ADCC). Moreover, mogamulizumab has the capacity to remove CCR4+ regulatory T cells, which can counteract regulatory T cell–mediated immune suppression. This therapy appears to be most efficacious in the setting of leukemic CTCL before the development of bulky lymph nodes or skin tumors. More recent anecdotal reports have described using mogamulizumab in a multimodality approach with interferon, which is known to enhance ADCC, as well as with photopheresis.

The most common adverse effects of mogamulizumab in the pivotal clinical trial were infusion reactions, drug rashes, diarrhea, and fatigue. Other adverse events such as pyrexia and cellulitis occurred in 41% of patients, but only one patient experienced grade III pyrexia. There were two deaths from sepsis and polymyositis that were possibly related to treatment.

Anti-PD1

PD-1 is expressed by activated T cells, on which it mediates T cell exhaustion and immune tolerance. It is often highly expressed on Sézary cells. Binding of PD ligand 1 (PD-L1) to PD-1 on T cells limits T cell proliferation and function and may produce T cell anergy. A phase II trial using pembrolizumab in 24 patients with advanced refractory CTCL had an overall response rate of 38%, including 2 complete responses. Responses were long-lasting with a median duration not reached at trial conclusion. Nivolumab has also demonstrated efficacy in early studies and case reports, including a phase I trial with an overall response rate of 15% among 13 patients with mycosis fungoides as well as a case report of a favorable response in a patient with refractory SS. Currently, studies are underway to better evaluate the safety and efficacy of combining PD-1 inhibitors with other therapies such as IFN-γ. The side effects of anti-PD1 treatment in CTCL are largely similar to those documented in treatment of other malignancies.

Anti-CD47

CD47 is a glycoprotein expressed on many normal cells that inhibits phagocytosis by macrophages via interaction with signal regulatory protein–α on the macrophage. On Sézary cells, the expression of CD47 is significantly increased. In recent studies by Johnson et al, a decoy receptor called TTI-621 has been administered intravenously to patients with SS, resulting in a marked decline of circulating Sézary cells. Observed side effects of anti-CD47 therapy have been minor, including fatigue, chills, decreased appetite, headache, and pruritus. Because TTI-621 mediates a prominent component of its effect via ADCC, agents that enhance this arm of cell-mediated immunity, such as IFN-α, can prominently increase in vitro destruction of the malignant T cells.

Chimeric antigen receptor T cells

The success of chimeric antigen receptor (CAR) T cells in B cell malignancies has raised expectations for these therapies in other cancers, including CTCL. A CAR is a synthetic surface receptor that combines extracellular antibody fragments for target cell recognition with intracellular T cell activation and costimulation domains. Patient T cells are derived from leukapheresis products, transduced with the CAR gene, and reinfused into the patient where they selectively lyse antigen-positive tumor cells.

For CTCL, one CAR-T strategy is targeting universal T cell antigens. Initially, the expression of CARs specific for the pan-T antigens CD3 and CD7 led to the fratricide of CAR-T cells, precluding their ex vivo manufacturing. However, deleting these antigens from CAR-T cells can eliminate fratricide and allow creation of a functional product. Interestingly, a CAR targeting CD5 did not lead to CAR-T fratricide.
cells are now being evaluated in clinical trials for T cell malignancies (clinicaltrials.gov studies NCT03081910 and NCT03690011).

More tumor-restricted antigens targeted with CAR-T have included CCR4, CD4, and CD30. A CAR targeting CCR4 eradicated xenografted CTCL and adult T cell leukemia tumors in mice. The targeting of CD4 led to fratricide of CD4+ CAR-T cells, but the CD8+ CAR-T cells remained and may have therapeutic potential. CD30-directed CAR-T has produced impressive responses in clinical trials for Hodgkin lymphoma, and this strategy is promising for CD30+ CTCL. The targeting of the clonal malignant TCR is another intriguing strategy. One approach is to use CARs specific for the TCR beta chain constant regions TCRB1 or TCRB2. As T cells express only 1 of these 2 genes, this may target tumor cells while preserving the benign T cell repertoire. This approach is being evaluated in a phase I/II clinical trial for T–non-Hodgkin lymphomas (clinicaltrials.gov study NCT03590574).

MULTIMODALITY IMMUNOTHERAPY

At our own and other cutaneous lymphoma programs, multimodality immunotherapy regimens have become the standard of care for patients with advanced CTCL. In the multimodality approach, we usually “layer on” additional therapies rather than replacing a single therapy that does not work. For example, we often initially treat patients with stage IVA SS with a combination of IFN-α, photopheresis, and skin-directed treatments. If a poor response occurs during the first 4 months, we typically add bexarotene and sometimes IFN-γ as well. Many of our patients experience significant clinical improvement with this regimen. If they do not, we may add mogamulizumab or low-dose (12 Gy) TSEBT. Through this approach, we have recently learned that addition of low-dose TSEBT to multimodality immunotherapy may lead to long-term remissions for some patients with refractory SS. Only after failure of this immunostimulatory approach do we consider histone deacetylase inhibitors, pralatrexate, brentuximab, alemtuzumab, and other accepted therapies that blunt the immune response. In the setting of rapidly progressive disease or in preparation for stem cell transplantation, chemotherapeutics are considered an acceptable approach.

CONCLUSION

In conclusion, the second article in this continuing medical education series reviewed the major immune-augmenting therapies available for patient with CTCL. Among established therapies, interferons, photopheresis, and retinoids have reliably demonstrated efficacy in the treatment of CTCL. New immunotherapeutic therapies, such as IL-12, TLR-agonists, monoclonal antibodies, and CAR-T, have displayed promise in clinical trials or are in development. Unlike immunosuppressive alternatives, these immune-potentiating modalities do not raise the risk of serious infection or hinder the ability to induce long-term remissions. It is recommended that immunotherapies be used in the initial management of advanced CTCL and in successive combination with each other for optimal outcomes.

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