Immunotherapy for Cutaneous T-Cell Lymphoma

18

Badri Modi, Francine Foss, Richard L. Edelson, and Michael Girardi

Introduction

The immunopathophysiology of CTCL has made it a favorable target for immunotherapy treatments. Prior to the development of extracorporeal photopheresis (ECP) in 1987, the first-line treatment for CTCL was nonspecific chemotherapy and offered a very poor response rate. The elucidation of the immune dysregulation seen in the disease not only spurred the introduction of biologic therapies such as interferons (IFNs), interleukins, and toll-like receptor (TLR) agonists, but also led to the investigation of the immunomodulatory impact of the other systemic therapies, such as retinoids and histone deacetylase inhibitors (HDIs), not traditionally classified as immunotherapy.

In review of the various available immune influencing treatment modalities and biologic agents for CTCL, we have considered their capacity to stimulate the immune system and restore a normal immunologic environment. The following sections include a discussion on the immune rationale, clinical efficacy, and combination regimens available for each therapeutic modality.

B. Modi • R.L. Edelson • M. Girardi
Department of Dermatology, Yale University School of Medicine, New Haven, CT, USA

F. Foss (✉)
Department of Medical Oncology/Hematology, Yale University School of Medicine, 333 Cedar Street, FMP 130, PO Box 208032, New Haven, CT, USA 06520
e-mail: Francine.foss@yale.edu

Extracorporeal Photopheresis

Although the exact mechanism of action is not yet elucidated, ECP therapy is regarded as an immunotherapy supported by several clinical studies and laboratory models, as well as the subsequent discoveries of clinical benefit in other T-cell-mediated diseases (e.g., graft-versus-host disease, organ transplant rejection). During the ECP procedure, the patient undergoes discontinuous pheresis cycles to harvest the leukocyte-rich buffy coat. The separated leukocytes are exposed to 8-methoxypsoralen (8-MOP) and irradiated with UVA light before reinfusion back into the patient. 8-MOP is a photoactivated, DNA-intercalating agent that forms cross-links after UVA-activation and induces apoptosis, particularly within activated and proliferating T cells.

The earliest clues to support the immunomodulating effects of ECP appeared in the initial clinical trial by Edelson et al [1]. The original goal of ECP was simply to induce CTCL cells to undergo apoptosis and reduce tumor burden. However, given that only a minor portion of total circulating T cells undergo extracorporeal treatment, it was evident that there must be another process in play, perhaps involving antigen presentation of apoptotic tumor cells. ECP's effects on circulating leukocytes appear to selectively target lymphoma cells. CTCL patients treated

F. Foss (ed.), *T-Cell Lymphomas*, Contemporary Hematology,
DOI 10.1007/978-1-62703-170-7_18,

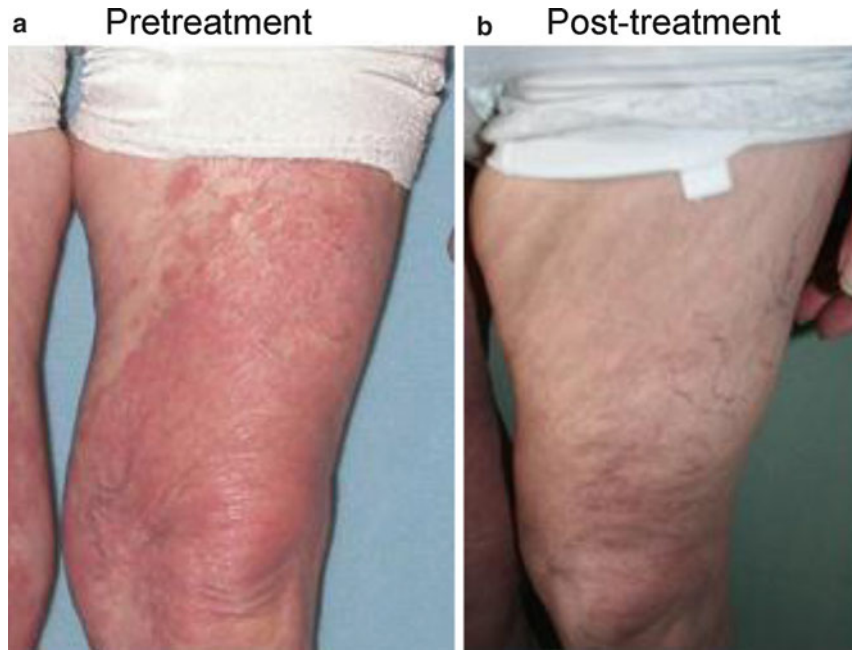

Figure 18.1 Patient with Sezary syndrome before (A) and six months after (B) extracorporeal photopheresis. Treatment was administered for two consecutive days every 4 weeks.

with ECP maintain their absolute number of normal T cells with a disproportionately greater decrease in their total body burden of malignant T cells. In addition, response rates to ECP are higher in individuals with normal or near normal natural killer and cytotoxic T-cell numbers and function [2]. ECP has also been shown to increase the production of TNF-α and shift the balance of Th1 and Th2 cytokines. Taken together, these data suggest that ECP induces an antitumor cellular immune response.

The mechanisms by which ECP cultivates an adaptive immune environment have recently been explored. As the patient's blood passes through the photopheresis apparatus, monocytes appear to be stimulated to mature into antigen presenting dendritic cells. Flow cytometric and DNA microarray analyses of passaged monocytes demonstrate an increased expression of dendritic cell markers [3]. Furthermore, these dendritic cells are functional in vitro in their capacity to stimulate allogeneic CD4+ T cells to proliferate as well as differentiate CD8+ T cells into cytotoxic cells. Thus, ECP-generated dendritic cells have the ability to ingest the apoptotic malignant T cells, ultimately leading to the potential production and reinfusion of putative CTCL tumor-loaded APC. These cells may therefore stimulate the production of specific antitumor cytotoxic T cells against the malignant lymphocytes.

The initial multicenter trial of erythrodermic patients demonstrated a 73% response rate, with a quarter of patients experiencing full remission. Their protocol consisted of two consecutive days of ECP treatment, repeated every 4 weeks. Figure 18.1 shows a representative patient with Sezary syndrome who had a complete clinical response. Since then, there have been approximately 30 trials of varying stages of CTCL that clinically confirm the benefit of ECP as monotherapy—in more than 1,000 patients treated worldwide with ECP, the response rate ranges from 43–100% with a complete response in 0–62% of patients [4]. Further investigation revealed a set of prognostic factors that predict a better response to ECP and include (1) absence of tumor-stage skin lesions, (2) shorter disease course, (3) absence of significant internal organ

involvement or bulky lymphadenopathy, and (4) minimal pretreatment with chemotherapy [2, 5].

A minority of patients treated with ECP monotherapy will be refractory to the disease, and it is important to consider the addition of other broad therapeutic categories, including skin-directed therapies, biologic response modifiers, and low-dose chemotherapy. Skin-directed therapies are thought to significantly enhance response rates by reducing tumor burden. These include radiotherapy, psoralen plus ultraviolet A (PUVA), and topical chemotherapy. Wilson and colleagues investigated the combination of ECP and total skin electron beam therapy (TSEBT) and found significantly longer progression-free survival periods and decreased CTCL-related mortality, compared to TSEBT alone [6]. Furthermore, skin-directed therapies are an obvious choice in patients who develop patch or plaque lesions after ECP initiation, as improving erythroderma often unveils cutaneous disease.

Biologic response modifier agents include cytokines, retinoids, and toxin–cytokine fusion proteins, and each is approved as a monotherapy for CTCL. Several retrospective studies comparing ECP and ECP plus biologic response modifiers suggest higher clinical response rates and longer survival in the combination cohort [7]. The addition of IFNα (3–18 MU (million units), three times per week) to ECP showed significantly improved response rates compared to ECP alone [8, 9]. The retinoid etretinate combined with ECP therapy in patients with recalcitrant palmer and plantar hyperkeratosis in erythrodermic CTCL results in marked improvement in the hyperkeratosis [10]. Similar favorable results are observed with the use of bexarotene, an RXR-specific retinoid. A small number of patients showed promising results after the combination of ECP and granulocyte-macrophage colony-stimulating factor (sargramostim) treatment. Finally, the combination of ECP and two other agents (IFNs, retinoids, GM-CSF) has been investigated in 28 patients with SS, achieving an overall response rate of 89% [2].

Although chemotherapy as a single agent has not been shown to improve response rates, combination of ECP and chemotherapy is shown to be beneficial to CTCL patients. As the disease advances, chemotherapy is thought to exacerbate immunosuppression in patients with an already blunted immune system. In the setting of ECP where cell-mediated immune response thrives, the introduction of apoptosis-inducing agents like chemotherapy may enhance the development of an antitumor response. The combination of ECP and low-dose methotrexate at 15–25 mg per week has been shown to be safe and enhance efficacy [11].

In conclusion, ECP is a rigorously studied and widely accepted monotherapy for patients with erythrodermic CTCL, which derives a significant portion of its clinical efficacy by modulating the body's natural immune system. ECP has a very limited side effect profile, and the major contraindication to its use is related to the ability of the patient's cardiovascular system to sustain the hemodynamic challenges posed by ECP cycles. With several small-scale, prospective studies suggesting the benefit of ECP in combination with other therapeutic categories, there is an obvious need for further investigation to clearly demonstrate these effects. As basic science models continue to explore the immunomodulatory mechanisms, it will both improve the efficacy of ECP and suggest novel approaches for the treatment of CTCL.

Cytokine-based therapy: Interferons and Interleukins

IFNα and IFNγ

The role of IFNs in innate immunity, immunomodulation, and cancer has been of great scientific interest. IFN alter the interaction between the body's own immune system and tumor cells, and in CTCL, play an important role in boosting antitumor immunity. They are normally secreted by a variety of cells—for example, lymphocytes, fibroblasts, epithelial cells, activated T cells, and natural killer cells—all of which express TLRs on their surface membranes or on internal endosomes. TLR ligands—including viral, bacterial, fungal products—naturally induce synthesis of

IFNs that can bind to specific receptors and cause antiviral, immunoregulatory, and antitumor effects. IFNs are a large family of secreted proteins classified into three different types, each of which has its own receptor targets and causes activation of unique signaling pathways. Th1 CD4+ T-helper cells secrete IFNγ, which activates cytotoxic CD8+ T cells and NK cells. IFNα directly inhibits the secretion Th2 cytokines, including IL-4 and IL-5 [12]. Also, IFNs prime plasmacytoid DCs for antigen presentation by upregulating MHC II expression and enabling effector CD8+ T cells for antigen recognition by upregulating expression of MHC I genes [13]. These immunomodulatory effects may help offset the Th1/Th2 imbalance characteristic of CTCL and restore cell-mediated immunity, providing the rationale for its use as therapy.

IFN-α, IFN-β, and IFN-γ represent the majority of IFNs that have been used as therapy for CTCL. The two most commonly used commercially available synthetic IFNs are IFN-α2a and IFN-α2b, both of which are injected subcutaneously. There have been at least 14 trials that demonstrate the clinical efficacy of IFN-α, examining various doses and dosing schedules; however, no consensus exists regarding which treatment regimen is most effective. The earliest trial, by Bunn and coworkers in 1984, delivered high doses of 50 MU TIW and resulted in clinical responses, but also substantial toxicities [14]. A subsequent trial comparing 3–36 MU per day confirmed that response rate is dose dependent [15], and 18 MU is generally considered the highest tolerable dose. In the largest trial examining IFN monotherapy, 43 patients with all stages of disease underwent a 12-week dose-escalation phase starting at 3 MU per day, followed by a 6-month maintenance phase at the maximal tolerated dose TIW. A partial response was observed in 49% of patients, and a complete response in 26% [16]. Thus, in order to optimize clinical efficacy and reduce toxicity, it is recommended to initiate treatment at 1 MU per day and escalate to 5 MU until a response or a dose-limiting side effect is observed. Patients who achieve remission are advised to continue treatment for 3 months beyond the last signs of disease, while a second agent may be introduced to patients who fail to achieve a response at the maximal tolerated dose [17]. IFN can also be administered directly into skin lesions, as intralesional injections are reported to have maximal benefit in both the injected and non-injected lesions [18]. Unlike other therapies, clinical stage at initiation is not a significant predictor of response, although patients with tumor-stage disease typically benefit less from IFN [17, 19]. Furthermore, an antibody reaction has been observed against synthetic IFNs and may blunt the therapeutic response [20]. Although there is no consensus yet about the clinical relevance of these antibodies [21], neutralizing antibodies may represent a mechanism of resistance and explain refractory disease in the setting of IFN therapy [22].

Iatrogenic elevation of inflammatory cytokines causes both immediate and long-term effects. Acutely, IFN therapy may induce a "flu-like" syndrome of fever, chills, arthralgias, and myalgias, lasting for approximately 1 week. These symptoms can be mitigated with prophylactic acetaminophen or ibuprofen 1–2 h prior to IFN injection. Importantly, infection must be ruled out in all patients who present with fever, regardless of their medication list. Chronic use of IFNs may lead to cachexia characterized by weight loss, fatigue, and anorexia. Other concerning side effects of long-term use include hypothyroidism, depression, rhabdomyolysis, and cardiac toxicity. Thus, a thorough workup that encompasses endocrine, renal, hepatic, and cardiac systems is warranted prior to initiating IFN therapy [17, 23].

Several other IFN-based therapeutic strategies are currently being examined, including those to enhance IFN-γ and IL-12 levels. Important cytokines of the Th1 effector response, IFN-γ, and IL-12 offer many theoretical benefits to CTCL patients. The addition of IFNγ to patients on ECP has shown efficacy in early and late stage disease. While the use of IFNγ as a monotherapy is promising, it is limited due to pharmacokinetic shortcomings such as its short half-life [5]. Innovative strategies for cytokine delivery exploit genetically modified, non-pathologic viruses expressing IFNγ and have already been well tolerated in early phase trials [24, 25]. In addition, in a phase

II trial investigating recombinant IL-12 in early stage MF, a partial response was observed in 43% of patients. Although most adverse effects were mild to moderate, one patient in partial response died from severe hemolytic anemia, which may have been exacerbated by IL-12 therapy [26].

IL-2-directed therapies

Interleukin-2 is an important growth factor for most types of T cells. Antigen engagement with a CD4+ lymphocyte's T-cell receptor induces rapid production of IL-2 followed by expression of the high-affinity IL-2R, enabling selective expansion of only the antigen-activated T cells [27]. The IL-2R is composed of three subunits—CD25 (α), CD122 (β), and CD132 (γ). Any combination of subunits may be found on T cells, but receptors with all three have the highest affinity for IL-2. While less than 5% of PBMCs from a healthy volunteer express IL-2R, more than half of all CTCL patients have malignant lymphocytes that over express this T-cell growth factor receptor [28]. Thus, IL-2R offers an attractive therapeutic strategy for targeting tumor cells, and monoclonal antibodies like daclizumab have already been developed to exploit this pathway. Unfortunately, daclizumab lacked strong cytocidal activity in clinical trials, and therefore other strategies were needed to direct more cytotoxic activity to IL-2R positive cells [29].

Denileukin-diftitox (DD) addresses this need by fusing a recombinant IL-2 molecule with the cytotoxic subunit of the diphtheria toxin. Engagement with IL-2R leads to internalization via receptor-mediated endocytosis, and allows the diphtheria subunit to block protein synthesis and cause cell death [30]. Due to the theoretical requirement of IL-2R affinity, most clinical trials assessing the efficacy of DD have required that a significant percentage—usually greater than 20%—of lymphocytes are CD25 or CD122 positive. Prince et al. conducted a phase III, placebo-controlled, randomized trial on 144 patients with CD25+ CTCL who had less than three previous therapies. Patients were enrolled into one of the three arms: (1) placebo group, (2) 9 μg/kg/day DD, and (3) 18 μg/kg/day DD. While the treatment groups experienced response rates similar to reports from previous trials (9 μg/kg/day DD: PR = 26.7 and CR = 11.1; 18 μg/kg/day DD: PR = 40% and CR = 9.1; placebo group: PR = 13.6% and CR = 2.3%), this trial demonstrated that "clinical responses" can also occur in the placebo group without treatment, suggesting the potentially confounding role of the disease's waxing and waning natural history when investigating novel therapies [31].

The most common toxicity observed in the DD clinical trials was infusion-related hypersensitivity, which included fever, rash, hypotension, chest tightness, or shortness of breath and can be controlled with steroid pretreatment [32]. Physicians should be aware of vascular leak syndrome, characterized by increased vascular permeability, and resulting in extravasation of fluid and subsequent hypotension, hypoalbuminemia, and edema. Patients with liver disease are at higher risk because they are unable to compensate for albumin loss. Increased muscular intracompartmental pressure may lead to rhabdomyolysis.

Since clinical response hinges on IL-2R expression, strategies to upregulate IL-2R expression in the presence of DD therapy have been investigated. Bexarotene has clinical efficacy against CTCL as a monotherapy and is known to have anti-proliferative, pro-apoptotic, and immune-modulating effects. In preclinical trials, bexarotene upregulated the expression of CD25 and CD122 subunits on T-cell leukemia lines and enhanced their susceptibility to DD [33]. The phase I clinical trial to test the in vivo reproducibility of this finding enrolled 14 patients with progressive disease after one systemic therapy. DD 18 μg/kg/day × 3 days every 21 days was combined with daily oral bexarotene in a dose-escalation fashion (75–300 mg/day) to upregulate IL-2R. Of the 14 patients, including one patient who had previously been refractory to eight cycles of DD monotherapy, four patients (33%) each achieved a partial response and complete response. Notably, all four patients who achieved a complete response also demonstrated significant upregulation of CD25 expression after bexarotene treatment; CD25 expression increased in

only one out of four patients who experienced a partial response. A potentially negative effect of this combination regimen is upregulation of CD25 expression in normal cells, enhancing their susceptibility to DD [34].

TLR Agonists

TLRs represent a class of ten pattern-recognition receptors found on various cells that signal the presence of infection and direct the innate and adaptive immune system to mount a response against the antigen [35]. TLRs detect pathogen-associated molecular patterns and stimulate immune cells via the MyD88-dependent interleukin 1 receptor (IL-1R)−TLR signaling pathway, which leads to activation of the transcription factor NF-κB [36]. The TLRs most relevant to CTCL immunotherapy appear to be TLR 4, 9, 7, and 8. TLR4 is found on myeloid DCs and recognizes the lipopolysaccharides of Gram-negative bacteria cell walls, resulting in secretion of IL-12, IL-4, and TNFα. Similarly, specific sequences of unmethylated DNA highly present in to bacterial and viral genomes known as "CpG motifs" activate TLR9 on plasmacytoid DCs and induce a cytokine response consisting predominantly of IFNα. TLR7 and TLR8 are found on both DC types and play a role in detection of viral ssRNA [37, 38]. TLRs are a critical mediator of the Th1 effector response [35], and thus are an attractive target for CTCL therapy to mediate restoration of the cytokine profile balance.

Imiquimod is a synthetic agonist for TLR7 and stimulates the production of numerous Th1 cytokines, including IFNα, IFNγ, TNFα, and IL-12 [39]; for this reason, 5% topical cream has been used off-label for stage IA disease. Approved for the treatment of basal cell carcinoma, actinic keratosis and genital warts, imiquimod shows a benefit in cancer by facilitating induction of an antitumor cellular response and apoptosis in some tumor cells. Clinical uses have been anecdotal and limited to skin-directed therapy for patches/plaques of early stage disease, but have suggested a clinical benefit even in patients refractory to other early stage treatments, including PUVA and low-dose retinoids [7, 40].

Synthetic oligodeoxynucleotides contain regions of unmethylated CpG motifs (CpG ODN) and are an excellent example of the translation of immunobiology into targeted therapy for cancer. This class of compounds is well described in its ability to potently stimulate DC activation, differentiation, and production of cytokines. Intralesional injection's ability to generate antitumor cytotoxic T-cell responses and induce a response has been demonstrated in murine melanoma models [41] and in human basal cell carcinoma and melanoma [42]. Culturing PBMCs from CTCL patients in the presence of CpG ODNs resulted in marked induction of IFN-α and significant activation of NK cells and CD8+ T cells, as measured by CD69 expression, compared to PBMCs from normal donors. These data provide the rationale for the development of clinical trials assessing the therapeutic benefits of CpG ODNs for CTCL [42].

A phase I dose-escalation study in 28 patients with treatment refractory stage IB to IVA was conducted to evaluate the safety and efficacy of PF-3512676 (0.08–0.36 mg/kg), a novel member of class-B CpG ODNs that targets TLR9. Patients tolerated the 24 weekly injections well, experiencing mostly grade 1 or 2 adverse events. Notably, no patients developed autoimmune disease, a concern with any novel immunomodulatory therapy. Although this study was not designed to rigorously assess efficacy, response rates of 32% (11% CR, 21% PR) suggest a clinical benefit of this therapy [43]. Further investigation is warranted, including the possible combination of TLR-agonists with other modalities of treatment.

Immune considerations for other systemic therapies: Retinoids and HDAC inhibitors

Retinoids

Retinoids are derivatives of vitamin A widely used as topical and oral therapy for dermatologic conditions including psoriasis, acne, and

CTCL. Their clinical effects are mediated through interactions with the transcription factors retinoid A receptors (RAR) and retinoid X receptors (RXR). They impact cell cycle progression through the modulation of cyclins, CDKs, and cell cycle inhibitors [44], and are known to induce apoptosis in vitro in cancer cell lines, including immortalized cells from CTCL patients [45].

Although retinoids are not traditionally classified as immunotherapy, clear evidence exists regarding their immunomodulatory role in CTCL, and this effect may contribute to their therapeutic value. In the epidermis, retinoids stimulate Langerhans cells to upregulate expression of MHC II and CD11c molecules, and thereby enhance the capacity to present antigen and generate a T-cell-mediated immune response [46]. As mentioned previously, some retinoids augment T-cell expression of IL-2R, and this specific effect is exploited to increase target sites for combination therapy with DD [47, 48]. Moreover, retinoids have a significant impact on the Th1/Th2 imbalance seen in CTCL by enhancing production of Th1 cytokines. In the presence of monocytes and IL-2, retinoids induce both normal and malignant T-cells to secrete IFN-γ through an IL-12-dependent mechanism [49]. Additionally, retinoids enhance the cytotoxicity of natural killer cells and CD8+ T cells, boosting the depressed cellular immunity seen in CTCL [50, 51].

Clinical use of retinoids for CTCL patients has been successful and includes both topical and systemic formulation. Bexarotene 1% gel demonstrated a 44% overall response rate (8% complete response rate) in patients with refractory early stage disease when applied every other day [52]. Oral bexarotene has been evaluated in both early and late stage patients, showing 54% and 45% response rates, respectively, at a dose of 300 mg/kg/day [53, 54]. Side effects include hyperlipidemia, central hypothyroidism, and headaches. Potential resistance remains a concern in the long-term therapeutic properties of bexarotene and may be mediated via epigenetic silencing of RXR genes [55].

HDI

HDIs have shown promise in the treatment of hematologic malignancies, including CTCL. Histone deacetylases are involved in the remodeling of chromatin, which impacts the level of access to regions of DNA available to transcriptional machinery. These epigenetic modifications have the potential of exerting cancer-promoting effects through changes in expression of critical oncogenes or tumor suppressor genes. Moreover, these inhibitors have recently been shown to deacetylate numerous nonhistone substrates, resulting in several anticancer effects ranging from cell cycle arrest to angiogenesis reduction to immunomodulation [56]. Evidence suggests that histone deacetylases are overexpressed in CTCL [57], which has led to the inclusion of HDI in the arsenal of therapy against CTCL.

The mechanistic basis of benefit seen from HDI therapy in CTCL patients has also been investigated. Induction of apoptosis is a well-described effect of HDI in both CTCL cell lines and ex vivo malignant cells, and this process is thought to be mediated through regulation of p21 expression [58]. The precise immunological impact of HDI remains to be clarified, but various immune responses have been reported. HDIs seem to promote the restoration of the effector cytokine response balance. Both primary cells and immortalized cell lines from CTCL patients show a dramatic reduction in Th2 cytokines IL-10, IL-2, and IL-4 [59]. Furthermore, in response to HDI treatment, the cell line Hut78 upregulates IL-2R expression and is subsequently more susceptible to the treatment with DD, the cytotoxic IL-2 chimeric compound that can only gain access to cells via IL-2R [58, 60]. Moreover, in vitro and ex vivo data suggests that HDI suppress the cell-mediated cytotoxic immune response, providing rationale for the use of HDI in the treatment of autoimmune conditions [61]. While other CTCL therapies typically enhance NK cell activation and dendritic cell maturation, HDIs seem to impair this process and further weaken the overall immunologic status. Preliminary data suggests that addition of a more classic immunotherapy such as TLR agonist may

be able to overcome HDI-induced immunosuppression [62]. Even despite these effects on the immune system, HDI monotherapy leads to a clinical benefit in CTCL patients.

Vorinostat and romidepsin are two HDI therapies approved for the treatment of CTCL. The pivotal, multicenter trial of vorinostat enrolled 74 patients with stage IB or higher CTCL who were refractory or resistant to other therapies; treatment with 400 mg of oral vorinostat daily produced an overall response rate of 30%, consistent even in patients with advanced disease including Sezary syndrome and T3 (tumor) stage [63]. The efficacy of romidepsin was assessed in two clinical trials of patients with all stages of diseases, including a significant majority of patients with poor prognoses who were refractory to at least one other therapy and often two. Even with the inclusion of patients with advanced disease, a 34% overall response rate was reported in both trials [64, 65]. Although safe and effective, significant cardiovascular and hematological adverse effects were reported in the HDI clinical trials, but the precise risk associated with these drugs is not clear [66, 67].

References

1. Edelson R, Berger C, Gasparro F, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. N Engl J Med. 1987;316:297–303.
2. Knobler R, Barr ML, Couriel DR, et al. Extracorporeal photopheresis: past, present, and future. J Am Acad Dermatol. 2009;61:652–65.
3. Berger C, Hoffmann K, Vasquez JG, et al. Rapid generation of maturationally synchronized human dendritic cells: contribution to the clinical efficacy of extracorporeal photochemotherapy. Blood. 2010;116:4838–47.
4. Scarisbrick JJ, Taylor P, Holtick U, et al. U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. Br J Dermatol. 2008;158:659–78.
5. Lansigan F, Foss FM. Current and emerging treatment strategies for cutaneous T-cell lymphoma. Drugs. 2010;70:273–86.
6. Wilson LD, Jones GW, Kim D, et al. Experience with total skin electron beam therapy in combination with extracorporeal photopheresis in the management of patients with erythrodermic (T4) mycosis fungoides. J Am Acad Dermatol. 2000;43:54–60.
7. Suchin KR, Cucchiara AJ, Gottleib SL, et al. Treatment of cutaneous T-cell lymphoma with combined immunomodulatory therapy: a 14-year experience at a single institution. Arch Dermatol. 2002;138:1054–60.
8. Dippel E, Schrag H, Goerdt S, Orfanos CE. Extracorporeal photopheresis and interferon-alpha in advanced cutaneous T-cell lymphoma. Lancet. 1997; 350:32–3.
9. Wollina U, Looks A, Meyer J, et al. Treatment of stage II cutaneous T-cell lymphoma with interferon alfa-2a and extracorporeal photochemotherapy: a prospective controlled trial. J Am Acad Dermatol. 2001; 44:253–60.
10. Lim HW, Harris HR. Etretinate as an effective adjunctive therapy for recalcitrant palmar/plantar hyperkeratosis in patients with erythrodermic cutaneous T cell lymphoma undergoing photopheresis. Dermatol Surg. 1995;21:597–9.
11. Zackheim HS, Epstein Jr EH. Low-dose methotrexate for the Sezary syndrome. J Am Acad Dermatol. 1989;21:757–62.
12. Suchin KR, Cassin M, Gottleib SL, et al. Increased interleukin 5 production in eosinophilic Sezary syndrome: regulation by interferon alfa and interleukin 12. J Am Acad Dermatol. 2001;44:28–32.
13. Borden EC, Sen GC, Uze G, et al. Interferons at age 50: past, current and future impact on biomedicine. Nat Rev Drug Discov. 2007;6:975–90.
14. Bunn Jr PA, Foon KA, Ihde DC, et al. Recombinant leukocyte A interferon: an active agent in advanced cutaneous T-cell lymphomas. Ann Intern Med. 1984;101:484–7.
15. Olsen EA, Rosen ST, Vollmer RT, et al. Interferon alfa-2a in the treatment of cutaneous T cell lymphoma. J Am Acad Dermatol. 1989;20:395–407.
16. Papa G, Tura S, Mandelli F, et al. Is interferon alpha in cutaneous T-cell lymphoma a treatment of choice? Br J Haematol. 1991;79 Suppl 1:48–51.
17. Olsen EA. Interferon in the treatment of cutaneous T-cell lymphoma. Dermatol Ther. 2003;16:311–21.
18. Wolff JM, Zitelli JA, Rabin BS, Smiles KA, Abell E. Intralesional interferon in the treatment of early mycosis fungoides. J Am Acad Dermatol. 1985;13:604–12.
19. Springer EA, Kuzel TM, Variakojis D, Kaul K, Rosen ST, Roenigk Jr HH. Correlation of clinical responses with immunologic and morphologic characteristics in patients with cutaneous T-cell lymphoma treated with interferon alfa-2a. J Am Acad Dermatol. 1993; 29:42–6.
20. Steis RG, Smith 2nd JW, Urba WJ, et al. Resistance to recombinant interferon alfa-2a in hairy-cell leukemia associated with neutralizing anti-interferon antibodies. N Engl J Med. 1988;318:1409–13.
21. Itri LM, Sherman MI, Palleroni AV, et al. Incidence and clinical significance of neutralizing antibodies in patients receiving recombinant interferon-alpha 2a. J Interferon Res. 1989;9 Suppl 1:S9–15.

22. Olsen EA, Bunn PA. Interferon in the treatment of cutaneous T-cell lymphoma. Hematol Oncol Clin North Am. 1995;9:1089–107.
23. Rook AH, Kuzel TM, Olsen EA. Cytokine therapy of cutaneous T-cell lymphoma: interferons, interleukin-12, and interleukin-2. Hematol Oncol Clin North Am. 2003;17:1435–48. ix.
24. Dummer R, Hassel JC, Fellenberg F, et al. Adenovirus-mediated intralesional interferon-gamma gene transfer induces tumor regressions in cutaneous lymphomas. Blood. 2004;104:1631–8.
25. Heinzerling L, Kunzi V, Oberholzer PA, Kundig T, Naim H, Dummer R. Oncolytic measles virus in cutaneous T-cell lymphomas mounts antitumor immune responses in vivo and targets interferon-resistant tumor cells. Blood. 2005;106:2287–94.
26. Duvic M, Sherman ML, Wood GS, et al. A phase II open-label study of recombinant human interleukin-12 in patients with stage IA, IB, or IIA mycosis fungoides. J Am Acad Dermatol. 2006;55:807–13.
27. Gaffen SL, Liu KD. Overview of interleukin-2 function, production and clinical applications. Cytokine. 2004;28:109–23.
28. Foss FM, Borkowski TA, Gilliom M, et al. Chimeric fusion protein toxin DAB486IL-2 in advanced mycosis fungoides and the Sezary syndrome: correlation of activity and interleukin-2 receptor expression in a phase II study. Blood. 1994;84:1765–74.
29. Lansigan F, Stearns DM, Foss F. Role of denileukin diftitox in the treatment of persistent or recurrent cutaneous T-cell lymphoma. Cancer Manag Res. 2010;2:53–9.
30. Kadin ME, Vonderheid EC. Targeted therapies: Denileukin diftitox–a step towards a 'magic bullet' for CTCL. Nat Rev Clin Oncol. 2010;7:430–2.
31. Prince HM, Duvic M, Martin A, et al. Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma. J Clin Oncol. 2010;28:1870–7.
32. Olsen E, Duvic M, Frankel A, et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. J Clin Oncol. 2001;19:376–88.
33. Gorgun G, Foss F. Immunomodulatory effects of RXR rexinoids: modulation of high-affinity IL-2R expression enhances susceptibility to denileukin diftitox. Blood. 2002;100:1399–403.
34. Foss F, Demierre MF, DiVenuti G. A phase-1 trial of bexarotene and denileukin diftitox in patients with relapsed or refractory cutaneous T-cell lymphoma. Blood. 2005;106:454–7.
35. Medzhitov R. Toll-like receptors and innate immunity. Nat Rev Immunol. 2001;1:135–45.
36. Jurk M, Heil F, Vollmer J, et al. Human TLR7 or TLR8 independently confer responsiveness to the antiviral compound R-848. Nat Immunol. 2002; 3:499.
37. Krieg AM. CpG motifs: the active ingredient in bacterial extracts? Nat Med. 2003;9:831–5.
38. Heil F, Hemmi H, Hochrein H, et al. Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. Science. 2004;303:1526–9.
39. Martinez-Gonzalez MC, Verea-Hernando MM, Yebra-Pimentel MT, Del Pozo J, Mazaira M, Fonseca E. Imiquimod in mycosis fungoides. Eur J Dermatol. 2008;18:148–52.
40. Dummer R, Urosevic M, Kempf W, Kazakov D, Burg G. Imiquimod induces complete clearance of a PUVA-resistant plaque in mycosis fungoides. Dermatology. 2003;207:116–8.
41. Lonsdorf AS, Kuekrek H, Stern BV, Boehm BO, Lehmann PV, Tary-Lehmann M. Intratumor CpG-oligodeoxynucleotide injection induces protective antitumor T cell immunity. J Immunol. 2003; 171:3941–6.
42. Wysocka M, Benoit BM, Newton S, Azzoni L, Montaner LJ, Rook AH. Enhancement of the host immune responses in cutaneous T-cell lymphoma by CpG oligodeoxynucleotides and IL-15. Blood. 2004;104:4142–9.
43. Kim YH, Girardi M, Duvic M, et al. Phase I trial of a Toll-like receptor 9 agonist, PF-3512676 (CPG 7909), in patients with treatment-refractory, cutaneous T-cell lymphoma. J Am Acad Dermatol. 2010;63:975–83.
44. Tang XH, Gudas LJ. Retinoids, retinoic acid receptors, and cancer. Annu Rev Pathol. 2011;6:345–64.
45. Fontana JA, Rishi AK. Classical and novel retinoids: their targets in cancer therapy. Leukemia. 2002; 16:463–72.
46. Meunier L, Bohjanen K, Voorhees JJ, Cooper KD. Retinoic acid upregulates human Langerhans cell antigen presentation and surface expression of HLA-DR and CD11c, a beta 2 integrin critically involved in T-cell activation. J Invest Dermatol. 1994;103:775–9.
47. Kempf W, Kettelhack N, Duvic M, Burg G. Topical and systemic retinoid therapy for cutaneous T-cell lymphoma. Hematol Oncol Clin North Am. 2003; 17:1405–19.
48. Foss FM, Waldmann TA. Interleukin-2 receptor-directed therapies for cutaneous lymphomas. Hematol Oncol Clin North Am. 2003;17:1449–58.
49. Fox FE, Kubin M, Cassin M, et al. Retinoids synergize with interleukin-2 to augment IFN-gamma and interleukin-12 production by human peripheral blood mononuclear cells. J Interferon Cytokine Res. 1999;19:407–15.
50. Pigatto PD, Bersani L, Colotta F, Morelli M, Altomare GF, Polenghi MM. Effect of retinoids on natural killer cell activity. Arch Dermatol Res. 1986;278:507–9.
51. Gordy C, Dzhagalov I, He YW. Regulation of CD8(+) T cell functions by RARgamma. Semin Immunol. 2009;21:2–7.
52. Heald P, Mehlmauer M, Martin AG, Crowley CA, Yocum RC, Reich SD. Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. J Am Acad Dermatol. 2003;49:801–15.

53. Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II–III trial results. J Clin Oncol. 2001;19:2456–71.
54. Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol. 2001; 137:581–93.
55. Lin JH, Kim EJ, Bansal A, et al. Clinical and in vitro resistance to bexarotene in adult T-cell leukemia: loss of RXR-alpha receptor. Blood. 2008;112:2484–8.
56. Choudhary C, Kumar C, Gnad F, et al. Lysine acetylation targets protein complexes and co-regulates major cellular functions. Science. 2009;325:834–40.
57. Mercurio C, Minucci S, Pelicci PG. Histone deacetylases and epigenetic therapies of hematological malignancies. Pharmacol Res. 2010;62:18–34.
58. Piekarz RL, Robey RW, Zhan Z, et al. T-cell lymphoma as a model for the use of histone deacetylase inhibitors in cancer therapy: impact of depsipeptide on molecular markers, therapeutic targets, and mechanisms of resistance. Blood. 2004;103:4636–43.
59. Tiffon C, Adams J, van der Fits L, et al. The histone deacetylase inhibitors vorinostat and romidepsin down-modulate IL-10 expression in cutaneous T-cell lymphoma cells. Br J Pharmacol. 2011;162:1590–602.
60. Shao RH, Tian X, Gorgun G, Urbano AG, Foss FM. Arginine butyrate increases the cytotoxicity of DAB(389)IL-2 in leukemia and lymphoma cells by upregulation of IL-2Rbeta gene. Leuk Res. 2002; 26:1077–83.
61. Wang L, de Zoeten EF, Greene MI, Hancock WW. Immunomodulatory effects of deacetylase inhibitors: therapeutic targeting of FOXP3+ regulatory T cells. Nat Rev Drug Discov. 2009;8:969–81.
62. Kelly-Sell M BB, Kim Y, Harrison C, Sutherland K, Showe L, Maria W, Rook A. The histone deacetylase inhibitor, romidepsin, suppresses in vivo immune functions of cutaneous T-cell lymphoma patients. J Invest Dermatol. 2011;131:Suppl; abstr 520.
63. Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol. 2007;25:3109–15.
64. Piekarz RL, Frye R, Turner M, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. J Clin Oncol. 2009;27:5410–7.
65. Whittaker SJ, Demierre MF, Kim EJ, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol. 2010;28:4485–91.
66. Bates SE, Rosing DR, Fojo T, Piekarz RL. Challenges of evaluating the cardiac effects of anticancer agents. Clin Cancer Res. 2006;12:3871–4.
67. Piekarz RL, Frye AR, Wright JJ, et al. Cardiac studies in patients treated with depsipeptide, FK228, in a phase II trial for T-cell lymphoma. Clin Cancer Res. 2006;12:3762–73.