Chapter 3

Treatment of Cutaneous T-cell Lymphoma

GürkanYardımcı[1]* and ZekayiKutlubay[2]*

[1]Istanbul Medipol University, Health Care Practice & Research Center, Esenler Hospital, Turkey
[2]Istanbul University, Cerrahpaşa Medical Faculty, Turkey

***Corresponding Author:** GürkanYardımcı, Istanbul Medipol University, Health Care Practice & Research Center, Esenler Hospital, Istanbul, Turkey, Email: dr.gurkanyardimci@gmail.com
ZekayiKutlubay, Istanbul University, Cerrahpaşa Medical Faculty, Istanbul, Turkey, Email: zekayikutlubay@hotmail.com

First Published **November 03, 2017**

Abstract

Cutaneous T-cell lymphoma is a mostly non-curative disease that is characterized by infiltration of malignant T lymphocytes in the skin. In the early stage, only skin involvement is observed, however, in advanced stage, peripheral blood and visceral organs can also be involved. The choice of treatment usually depends on the stage. Although skin-directed therapies are often the first choice for patients with early-stage, systemic therapies alone or in combined with skin-directed therapies should be used in the treatment of patients with advanced-stage.

Keywords

Cutaneous Lymphoma; T-Cell; Skin-Directed Therapy; Systemic Treatments

Introduction

Cutaneous T-cell lymphomas (CTCLs) represent a heterogeneous group of non-Hodgkin lymphomas (NHLs) characterized by infiltration of malignant monoclonal T lymphocytes in the skin [1]. CTCLs are account for more than two-thirds of all primary cutaneous lymphomas [2]. Based on the Surveillance, Epidemiology, and End Results (SEER) data, the incidence of CTCL is 7.7/1000000 person-years. Men are more often affected than women (male-to-female ratio, 1.7:1) [3]. The most common age range of CTCL varies between 55 and 60 years [1].

Although a number of pathogenetic mechanisms have been reported, the etiopathogenesis of CTCL is still unknown. It may not always be easy to diagnose CTCL. Misdiagnoses are common in patients with CTCL, especially during early-stages. In most cases, the time to diagnose CTCL is an average of 6 years from the onset of skin lesions [1].

A consensus classification for cutaneous lymphomas was published by World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC) in 2005 [4]. According to this classification, CTCLs are classified into different types such as mycosis fungoides (MF), MF variants and subtypes, Sézary Syndrome (SS), adult T-cell leukemia/lymphoma, primary cutaneous CD30 (+) lymphoproliferative disorders, subcutaneous panniculitis-like T-cell lymphoma, extranodal NK/T-cell lymphoma (nasal type), primary cutaneous peripheral T-cell lymphoma, unspecified. These are listed in Table 1. A new classification of lymphoid neoplasms was revised by WHO in 2016 [5].

MF is the most common form of CTCL that is characterized by patches and plaques in early-stage of disease and tumors and erythroderma in advanced-stage of disease. SS is an aggressive form of CTCL that is characterized by exfoliative erythroderma, lymphadenopathy, and leukemic blood involvement [6,7].

Table 1: WHO-EORTC classification of cutaneous lymphomas with primary cutaneous manifestations.*

Cutaneous T-celland NK-celllymphoma
• Mycosisfungoides
• MF variantsandsubtypes Folliculotropic MF Pagetoidreticulosis Granulomatousslack skin
• Sézarysyndrome
• Adult T-cellleukemia/lymphoma
• Primarycutaneous CD30+ lymphoproliferativedisorders Primarycutaneousanaplasticlargecelllymphoma Lymphomatoidpapulosis
• Subcutaneouspanniculitis-like T-celllymphoma
• Extranodal NK/T-celllymphoma, nasaltype
• Primarycutaneousperipheral T-celllymphoma, unspecified Primarycutaneousaggressiveepidermotropic CD8+ T-celllymphoma (provisional) Cutaneousγ/δ T-celllymphoma (provisional) Primarycutaneous CD4+ small/medium-sizedpleomorphic T-celllymphoma (provisional)
Cutaneous B-celllymphomas
• Primarycutaneousmarginalzone B-celllymphoma
• Primarycutaneousfolliclecenterlymphoma
• Primarycutaneousdiffuselarge B-celllymphoma, legtype
• Primarycutaneousdiffuselarge B-celllymphoma, other Intravascularlarge B-celllymphoma
Precursorhematologicneoplasm
• CD4+/CD56+ hematodermicneoplasm (blastic NK-celllymphoma)

i* Data taken from reference 4.

There is currently no known cure for CTCL. Treatment options are generally classified into two groups: skin-directed therapies and systemic therapies. Skin-directed therapies are usually preferred as the first choice for patients with early-stage disease (stage IA to IIA). Whereas, systemic therapies are often preferred both in refractory patients with early-stage and in patients with advanced-stage (≥ stage IIB). Thus, staging of the disease is very important for treatment choice [1].

Patients with early-stage disease have often an indolent course, but progression can occur in approximately 25% of the patients [8,9]. In early-stage, the main goals of treatments are to maximize patient comfort, reduce disease burden, and minimize treatment toxicities [1,9]. Expectant management may be acceptable in selected patients. However, most of the patients are treated with skin-directed therapies with or without systemic treatments. Skin-directed treatment options include emollients, topical steroids, topical retinoids, topical chemotherapy, psoralen plus ultraviolet A (PUVA) phototherapy, ultraviolet B (UVB) phototherapy, total skin electron beam therapy (TSEBT), and local radiotherapy [9,10].

Although skin-directed therapies are often the first choice in early-stage disease, these treatments are insufficient in advanced-stage disease. Combination of systemic and skin-directed therapies has been preferred in patients with advanced-stage [6]. The treatment of advanced-stage

requires a multidisciplinary approach, including hematologists/oncologists, dermatologists, and radiation oncologists [9].

Treatment Options

Expectant Policy (Watch and Wait)

The expectant policy is only recommended in carefully selected stage IA patients with MF/SS. Because in these patients, the risk of progression of disease is very low, which has been estimated to be 10% within 10 years. In 2017, this management option is still present in the updated recommendations of EORTC consensus. All patients managed with expectant policy should be monitored against the progression of their disease and informed about their disease [10].

Skin-Directed Therapies

Emollients

Skin barrier tends to deteriorate in inflammatory skin diseases such as MF/SS. Transepidermal water loss (TEWL) occurs from the barrier-impaired skin and as a result, the skin becomes clinically dry, scaly, and itchy. Emollients, or moisturizers, prevent to TEWL due to their occlusal properties. Humectants also increase the water-holding capacity of the stratum corneum by absorbing water from the surrounding tissue. Emollients contribute to the reduction of skin dryness, scaling, and symptoms

of pruritus through these mechanisms. Glycerin is one of most commonly used humectants and its effectiveness has been shown. Although ointments are more occlusive and better moisturizers, the form of cream of emollients is recommended twice daily because of patient compliance [11].

Topical Steroids

Topical steroids have been used for about 60 years in the treatment of MF. They have both anti-inflammatory and anti-proliferative effects. Mechanisms of action include inhibition of phagocytosis, decrease in monocytic and lymphocytic activity, decrease in the level of chemical mediators such as interleukin (IL)-1, IL-2, interferon (IFN)-γ, tumor necrosis factor (TNF) and granulocyte-monocyte colony-stimulating factor (GM-CSF), reduction in mitotic activity, and increase in apoptosis of malignant cells [11].

Topical steroids may be effective for patients with patch-stage MF with <10% body surface area. This therapy can be combined with phototherapy methods such as narrow-band UVB or PUVA [12]. In a prospective study, 79 patients with MF were treated with topical class I to III corticosteroids. Of these patients, 51 were stage T1 (less than 10% of skin involved) and 28 were stage T2 (10% or more of skin involved). All patients used the topical steroids twice daily for at least 3 months. The median follow-up for all 79 patients was 9 months. The complete response rates (CRRs) were 63% and 25% in stage T1 and T2

patients, respectively. But overall response rate (ORR) was not significantly different with stage T1 (94%) compared to stage T2 (82%). Adverse effects included temporary depressions of the serum cortisol level, temporary minor irritation, localized cutaneous atrophy, and stretch marks [13]. *Liu* et al. reported that intralesional steroid injection was effective in patients with treatment-resistance tumor stage MF. Focally resistant MF lesions were treated with intralesional triamcinolone at concentrations of 10mg/mL and 40mg/mL without severe adverse events [14]. Despite the satisfactory results, it should not be forgotten that relapse might develop after topical steroid therapy [1].

Mechlorethamine (Nitrogen Mustard)

Mechlorethamine is an alkylating agent that can be used in early stage CTCL. It inhibits quickly proliferating cells. Although it has been used for treatment of leukemic diseases since about 70 years, in 2013, the topical gel formulation was approved by Food and Drug Administration (FDA) for patients diagnosed with stage IA and IB MF-CTCL who have received prior skin-directed therapy. A different formulation, mechlorethamine ointment, has the similar efficacy with mechlorethamine gel, however, there are some disadvantages such as greasy, less stable, and more difficult to apply compared with gel formulation. After application of mechlorethamine gel, some adverse effects such as redness, inflammation, swelling, itchiness, blisters, secondary skin infections, ulceration, non-melanoma skin cancers may occur [15].

Mechlorethamine is recommended to the entire skin surface except face, intertriginous areas, and genitalia once or twice per day for optimal therapeutic effect. It can be compounded in both formulations at a concentration of 10-20 mg/dl [16]. Mechlorethamine gel should apply "a pea-size" amount until the patch or lesion is covered in a very thin layer. Sufficient amount of gel should be dried within 5 minutes. The skin area where gel will be applied should be clean, dry and intact; patients should be informed about avoiding application of mechlorethamine to the mucosa, open wounds, and skin folds. If any of the adverse events such as intense hyperpigmentation, erythema, swelling, increased sensitivity, blisters, ulceration, pain, or burning are noticed, mechlorethamine gel should be stopped or temporarily

discontinued. In such cases, topical corticosteroids could be applied. It is suggested that treatment should be continued within 1 month after the disease is cleared and then gradually decreased [17].

In a randomized, controlled, multi-center study, *Lessin* et al. reported that response rates for 0.02% mechlorethamine gel and ointment were 59% and 48%, respectively, in patients with early-stage MF. During the therapy, no severe adverse effects were reported. But within the additional 12-months follow-up period after the 12-months treatment, 20 non-melanoma skin cancers (9 squamous cell carcinomas, 10 basal cell carcinomas, and 1 Merkel cell carcinoma) were recorded in 11 patients. Only 6 of

non-melanoma skin cancers were detected in the treatment areas [18].

Carmustine

Carmustine, also known as bichlor ethylnitrosourea (BCNU) is an alkylating agent and it has not yet approved by the FDA [11]. It is preferred less frequently than mechlorethamine. It is available in two different forms (aqueous solution or ointment base) at a concentration of either 10 or 20 mg/dl. It is recommended to apply once daily [16].

In one study, 13 patients with stage IA-IIIB folliculotropic MF treated with topical carmustine 0.04% ointment for an average of 12 months. In 9 patients, topical carmustine was used in combination with low-dose IFN-α or IFN-γ at 1-2 million units 3 times weekly or low-dose isotretinoin at 10-20 mg daily. The remaining 4 patients were treated with topical carmustine as monotherapy. Of 13 patients, 6 achieved complete response and 7 patients achieved partial response. Telangiectasia was the only adverse event in patients treated with topical carmustine [19].

Topical Retinoids

Retinoids, a group of vitamin-A derived compounds, play important roles in some biological processes, especially during cellular differentiation, proliferation, and apoptosis. These biological effects are the result of interactions with intracellular retinoic acid receptors (RAR) and

retinoid X receptors (RXR). But the exact mechanism of retinoids is still unknown in CTCL [11]. There are 3 different topical retinoids including bexarotene, tazarotene, and alitretinoin are available for treatment of CTCL.

Bexarotene, also known as rexinoid, is a retinoid X receptor-selective ligand [10, 20]. Both systemic therapy (see below) and topical gel formulation is available [10]. In 2000, 1% gel formulation of bexarotene was approved by the FDA for topical treatment in patients with CTCL (stage IA and IB) who have refractory or persistent disease after other therapies or who have not tolerated other therapies [10, 11]. In phase I and II open-label trial, efficacious results were noted with bexarotene gel in 67 patients with stage IA-IIA CTCL. ORR was 63%, while clinical complete response was 21%. Median projected time to onset of response and the estimated median response duration from the start of therapy were 20.1 and 99 weeks, respectively. Patients with no previous therapy for MF had higher response rate (75%) compared to patients who previously underwent topical therapies (67%) [20].

Unlike bexarotene, tazarotene binds to RAR-β and –γ subtypes [11,21]. Although it was approved by the FDA for the treatment of patients with psoriasis and acne vulgaris, it has not yet been approved in the treatment of CTCL [21]. In an open-label, prospective study of tazarotene 0.1% cream as monotherapy for stages IA to IIA CTCL, CRR was reported as 60% [22]. *Apisarnthanarax* et al. also reported that 58% of patients was achieved at least

a moderate (>50%) global improvement in body surface area after treatment with tazarotene gel 0.1% once daily for 24 weeks [23].

Alitretinoin can binds to both RAR and RXR receptors [11]. A case reported that alitretinoin gel 0.1% was effective in a tumoral lesion of patient with CTCL [24].

Phototherapy

Phototherapy was firstly used for MF in the form of PUVA in 1976. Later, broad-band UVB, narrow-band UVB, extracorporeal photopheresis (ECP), photodynamic therapy, UVA-1 therapy, and excimer laser treatment were used for patients with MF. These treatment modalities except PUVA and UVB phototherapy have not found widespread application in MF [25]. PUVA photochemotherapy or narrow-band UVB phototherapy is still the first-line treatment option for patients with early stage MF. It can be used not only as monotherapy but also as combination therapy with systemic treatments, especially in patients with refractory MF or advanced MF [26]. Although phototherapy has long been used in the treatment of CTCL, a comprehensive guideline was published by the United States Cutaneous Lymphoma Consortium (USCLC) in 2016 [27].

Although numerous drugs have been developed in recent years, PUVA still mainstays an important position in the treatment of MF, especially in early-stage of the disease [25]. In PUVA therapy, oral psoralen, known as 8-meth-

oxypsoralen (8-MOP), should be taken at dose 0.5 mg/kg 1-1.5 hours before exposure to UVA. PUVA is usually recommended 2 or 3 times a week [26]. In a retrospective study, 28 patients with stage IA-IVA MF were treated with PUVA twice or three times weekly. Complete response was noted in 64% of patients, while partial response was 21%. The median relapse-free interval was 10 months in PUVA-treated group [28]. *Reidel* et al. was first reported the efficacy and safety of cream PUVA in MF patients. A total of 14 lesions of 10 patients with patch- or plaque-type MF affecting less than 10% body surface area were treated with cream PUVA using the digital phototherapy device. In the 7 of 14 treated lesions, complete remission was observed after an average of 13.4 weeks and an average cumulative UV dose of 42.6 J/cm^2 in a mean of 31.2 treatment sessions [29]. There are few studies investigating the effectiveness of bath PUVA in patients with CTCL. *Pavlotsky* et al. investigated the effectiveness of bath PUVA in a study enrolled 14 patients with folliculotropic MF and 12 patients with narrow-band UVB-refractory early-stage MF. Patients treated with bath PUVA 3 times weekly. Complete clinical response was observed in 62% of patients after an average of 33 weeks. No severe side effects reported after the bath PUVA, reported side effects were mild burn/erythema, photosensitivity, PUVA lentigenes, and bath PUVA-induced pigmented strips [30].

Studies have shown that UVB phototherapy for MF is at least as effective as PUVA [31]. UVB phototherapy was firstly used in the treatment of MF in 1982 [25]. In

children with early-stage MF, narrow-band UVB phototherapy is recommended as the first-line treatment [32]. Narrow-band UVB is usually recommended 2 or 3 times a week, like PUVA. The starting dose may be determined according to the skin type or minimal erythema dose of the patient [26]. *Ahmad* et al. treated 12 patients with stage IA-IIB MF with narrow-band UVB three times weekly. The response to treatment was complete in 6 (50%) patients and partial in 4 (33%) patients. The median relapse-free interval was 11.5 months in narrow-band UVB treated group [28].

In both PUVA and UVB phototherapy, maintenance treatment is often required to maintain clinical control of disease. Adverse events of phototherapy include erythema, pruritus, stinging pain, photosensitivity, subungual hemorrhage, photoonycholysis, melanonychia, hypo/hyperpigmentation, photoaging, xerosis, conjunctivitis, keratitis, cataracts, and skin cancer [26].

Photodynamic therapy (PDT) with aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) can be an important alternative choice for localized forms of MF that responded poorly to regular treatments. The risk of toxicity accumulation of this non-invasive method is low, and it has excellent cosmetic results and selectivity. Negligible generalized photosensitivity and low carcinogenic potential are another advantages of PDT [33]. Efficacious results have been reported in patients treated with PDT [33,34]. In a novel, systematic review published by *Xue* et al., PDT was effective and well-tolerated in patients with

localized relapsed or refractory MF lesions, even in tumoral lesions [33]. *Han* et al. also reported the improvement of plaque lesions with ALA-PDT in 3 patients with plaque-stage MF who failed routine therapy. Plaque lesions of 2 patients were completely improved, while more than 75% improvement was observed in 1 patient [35].

Radiotherapy

Radiation therapy is a valuable treatment option for CTCLs because of radiosensitivity of lymphocytes [36]. It has been used in the treatment of CTCL for years and penetrates deeper skin layers compared with phototherapy [37]. According to the number of lesions and involvement surface of the skin, it can be used locally or entirely on the skin [36].

There are many reports showing that radiotherapy is effective in the treatment of CTCL [38-43]. Localized radiotherapy can be curative for patients with unilesional lesion. The patients with clinical stage IA MF are less than 5% of all patients with MF. In this subgroup, localized radiotherapy has excellent responses with 95% to 100% of lesions experiencing a complete response [36]. *Conill* et al. demonstrated the efficacy of radiotherapy for primary cutaneous lymphomas. In all of 27 patients, satisfactory results were observed. Of 27 patients, 13 were CTCL and complete response was 85% in these patients. In 24 of 27 patients, complete response was obtained in the irradiated lesions, while partial response was in 3 patients [44]. In

one study, 63 tumors in 56 patients with primary cutaneous anaplastic large cell lymphoma were treated with radiotherapy. The radiotherapy dose ranged from 6 to 45 Gy, with a median dose of 35 Gy and mode of 30 Gy. Complete clinical response was achieved in 60 of 63 tumors (95%) and partial response in 3 tumors (5%) [38].

In patients with all skin surface involvement, TSEBT is often preferred instead of localized radiotherapy [36, 37]. TSEBT has been used to treat patients with CTCL since 1951 [45]. This method can be used in all stages of MF and SS. Conventional dose of TSEBT is 30-36 Gy in various stages of MF and SS. The ORRs vary depending on the dose [37]. In a retrospective study, 45 patients with CTCL (26 MF cases, 10 SS cases, and 9 non MF/SS PCTCL cases) were treated with TSEBT. The ORRs were reported 92%, 70%, and 89% in MF patients, SS patients, and non-MF/SS PCTCL patients, respectively. The ORR was 92% in the MF patients treated with conventional dose (30-36 Gy) regimens, while the ORR was 75% in the MF patients treated with low-dose (<30 Gy) regimens. In the MF patients, the overall survival was 77 months with conventional dose regimens versus 14 months with low-dose regimens. In SS patients, the median overall survival was 48 versus 16 months, respectively. Median event-free survival for MF in conventional dose patients versus low-dose patients was 15 versus 8 months, respectively and 19 versus 3 months for SS patients [41]. In a cohort study, *Danish* et al. treated 68 patients with CTCL (13 patients CD30 (+) and 55 patients CD30 (-))¬ with rotational TSE

irradiation. After 6 weeks radiation therapy, complete clinical responses (>90% reduction of skin disease burden) were reported 85% and 81% in CD30 (+) and CD30 (-) cases, respectively. After 6 months of treatment, complete clinical responses were 23% and 50% in CD30 (+) and CD30 (-) cases, respectively [40].

Low-dose TSEBT may be an alternative therapy to conventional TSEBT. Compared to conventional dose therapy, low-dose TSEBT is associated with milder toxicities and lower complete response overall [6]. In a nationwide cohort study, inadequate response was reported in 10 patients treated with low-dose (4 Gy) TSEBT compared to patients treated with high-dose (30 Gy). The ORR was 100% in patients treated with high-dose. CRRs were 68% and 10% in groups treated with high-dose and low-dose, respectively. Complete response occurred after a median time of 2.1 months in high-dose group and 11.5 months in low-dose group [43].

Acute side effects of radiotherapy include erythema, desquamation, and skin ulceration, while long-term side effects are pigmentary changes, alopecia, and rarely secondary skin cancers [36]. But adverse events of TSEBT are generally reversible and not severe and generally observed in skin, hair and nail. These adverse effects include fatigue, erythema, dry desquamation, blisters, hyperpigmentation, skin pain, skin infections, alopecia, loss of fingernails and toenails, hypo- or anhidrosis, radiation dermatitis, male gynecomastia, scattered telangiectasia, lower leg edema,

ocular irritation, and skin cancers such as squamous cell carcinoma and basal cell carcinoma [37,45].

Imiquimod

Imiquimod is a toll-like receptor (TLR)-7 agonist that causes cytokine release and inflammatory reaction [46]. Although there are no large series showing efficacy in the treatment of patients with MF, variable responses have been reported in small case series [46,47]. *Shipman* and *Scarisbrick* reported complete response with imiquimod in 1 patient with stage IB MF. However, one patient with stage IA MF was achieved partial response, while stable disease was observed in 1 patient with stage IA MF [46]. Imiquimod 5% cream was also found to be effective in 2 patients with tumor-stage MF without severe adverse events [47].

Systemic Therapies

Systemic Retinoids

As mentioned above, retinoids, which are structural and functional derivatives of vitamin A (retinol), have been used in various malignant diseases such as breast, ovarian, renal, head and neck, melanoma, prostate cancers, and hematologic malignancies as well as CTCL. The exact mechanism on tumorogenesis and cancer biology is still not clearly understood. Retinoids show their biological effects through nuclear receptors regulating gene transcription called RARs and RXRs. By binding to these receptors, retinoids induce the apoptosis mechanism and cause immunomodulatory changes [48].

In 1983, satisfactory results were reported in 4 patients with refractory MF with isotretinoin (13-cis-retinoic acid) at doses of 1 to 3 mg/kg per day. Near complete clearing of extensive tumors and plaques and partial improvement were observed in 1 and 2 patients, respectively. Although complete response was seen in 1 patient, relapse occurred after discontinuation of the drug [49]. Isotretinoin also showed beneficial effect for persisting cysts and comedonesin a patient with follicular MF [50].

Cheeley et al. reported treatment results of patients with CTCL treated with acitretin alone or combined with other therapies. Although ORR was 59%, stable disease and progressive disease were observed in 25% and 16% of remaining patients, respectively [51].

Bexarotene is the only FDA-approved retinoid in the treatment of CTCL [48]. Use of bexarotene has been reported as monotherapy or combined therapy in the treatment of various CTCLs [52,53]. In 2012, the United Kingdom Cutaneous Lymphoma Group (UKCLG) produced a consensus statement updating their 2003 guidelines on safe clinical prescribing of bexarotene for patients with CTCL [54].

In a novel, multicenter, open-label, historically controlled, single-arm phase I/II study, bexarotene was administrated once daily at a dose of 150mg/m^2 in 3 patients and at a dose of 300mg/m^2 in 13 Japanese patients. Stages of their diseases of the patients varied between stage IB and IIIA. At a dose of 150mg/m^2, partial response was

observed in 2 of 3 patients with MF, while stable disease process was observed in 1 of 3 patients with MF. At an initial dose of 300mg/m^2, overall skin response rate was reported 61.5%, while 2 of 13 patients had stable disease and 2 of 13 patients had progressive disease [52]. In 2007, *Gniadecki* et al. suggested a treatment algorithm for bexarotene in refractory CTCL. Bexarotene should be initiated at the lower dose of 150mg/m^2 per day for 2-4 weeks. If the lipid levels are normal after the initial dose, the dose is increased to the full optimal dose 300mg/m^2 per day. If there is a treatment response at 6 months after the start of bexarotene treatment, the duration of treatment should be extended by at least 6 months. In the case of stable, active, or progressive disease, treatment options that may be an alternative to bexarotene should be considered [55].

In a novel, prospective, phase II trial, 21 refractory and/or relapsed patients with MF were treated with oral low-dose bexarotene plus PUVA. The ORRs after induction phase and maintenance phase were observed 85.6% and 76.2%, respectively. Median event-free survival for the whole group was observed 31 months. Low and moderate grades adverse effects were usually observed with low-doses of bexarotene combined with PUVA [53].

Adverse effects of bexarotene include hyperlipidemia, central hypothyroidism, hepatitis, anemia, leucopenia, headache, nasopharyngitis, and skin peeling [52,55]. It has also been reported late-onset CD4 lymphopenia in a CTCL patient [56]. Bexarotene is contraindicated in preg-

nancy. Women of childbearing age should be warned of an effective contraception during the use of bexarotene. The use of bexarotene is not recommended in patients with a family history of hypertriglyceridemia [55].

In several case reports, alitretinoin was found to be effective in different subtypes of CTCL, including folliculotropic MF, pagetoid reticulosis, palmoplantar MF, and MF with CD30 (+) large cell transformation [57-61].

Systemic chemotherapy

Chemotherapy with single- or multi-drug treatments can be used for patients with CTCL [62-67]. This treatment is often preferred to treat advanced stage patients with disseminated bulky nodules, disseminated tumors, or visceral disease. This regimen is not curative for CTCL patients and induces immunosuppression. Although single-agent chemotherapy is effective, long-term remissions may not be achieved [68].

Systemic multi-agent chemotherapy with ESHAP (etoposide, cisplatin, high-dose aracytine, methylprednisolone) had low number of complete remissions and short duration of partial remissions. It had also high-grade toxicity including prolonged myelosuppression (91%) and infectious complications (82%) [63]. *Luo* et al. reported good response with one cycle of chemotherapy with vincristine sulfate, etoposide, L-asparaginase, and prednisone acetate (known as the VELP regimen) in a patient with

syringotropic MF who did not respond to UVB phototherapy [64].

Doxorubicin (also known as hydroxydaunorubicin, or Adriamycin) is commonly used for advanced CTCL as a part of CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone) regimen [69]. It is an active chemotherapeutic agent that has severe cardiac toxicity. Pegylated liposomal-encapsulated doxorubicin is a form of doxorubicin that has fewer cardiac side effects and can provide partial improvement for cutaneous lymphoma [70]. In a prospective, international, multicentre phase II trial of intravenous pegylated liposomal doxorubicin, ORR was 40.8%; 6.1% experienced complete clinical responses, and 34.7% experienced partial responses. Median time to progression and median duration of response were 7.4 and 6 months, respectively [66].

Gemcitabine is one of the chemotherapeutic agents in the treatment of CTCL [67,71]. In one study, 80% of patients demonstrated a reduction in modified Severity-Weighted Assessment Tool (mSWAT) score with 4 cycles of gemcitabine combined with bexarotene. At 12 and 24 weeks, the objective disease response was 31% and 14%, respectively [71]. *Buhl* et al. also reported excellent improvement after low-dose gemcitabine in patients with tumor-stage MF [67].

Systemic steroids, which are found in some multiagent chemotherapy regimens such as VELP and ESHAP,

can be effectively used either alone or in combined with cyclosporine in the treatment of CTCL, especially subcutaneous panniculitis-like T-cell lymphoma [72-74].

Interferons

Interferons that are both naturally occur in the human body as a part of innate immune system and produced by stimulated eukaryotic cells have antiviral, cytostatic, and immunomodulatory properties. Three different major types of IFN are available, known as IFN-α, IFN-β, and IFN-γ. IFN-α and IFN-γ are the more commonly used types in the treatment of CTCL [75].

IFN-α has been recommended in all stages of MF/SS for a long time. The first study to investigate the efficacy of IFN-α in CTCL was conducted in 1984 [75]. In prospective studies where IFN-α was used alone, CRRs were often low [76,77]. However, more successful results have been reported in patients treated with IFN when used in combination with treatments such as PUVA, acitretin, and TSEBT [75,78-84]. In a phase 2 trial, 63 patients with all stages of MF and SS were treated with IFN α-2a plus PUVA for 1 year. Complete response and partial response were observed in 74.6% and 6% of patients, respectively. The 5-year overall survival rate and 5-year disease-free survival rate were reported 91% and 75%, respectively. Although 5 patients could not continue the IFN α-2a therapy due to toxicity, no life-threatening side effects were observed [78].

In contrast to IFN-α, studies investigating the efficacy of IFN-γ in the treatment of CTCL are less common. IFN-γ is thought to be effective with effects on innate and adaptive immune system in the treatment of CTCL [75]. Like IFN-α, IFN-γ may be used both alone or in combined with other treatments such as bexarotene, ECP, TSEBT, vorinostat, and romidepsin in the treatment of CTCL [75,86].

Extracorporeal Photopheresis

ECP, also known as extracorporeal photochemotherapy, extracorporeal photoimmunotherapy, or photopheresis, is an apheresis-based therapy that is also used in the treatment of various diseases such as graft-versus-host disease, systemic sclerosis, inflammatory bowel diseases as well as CTCL. The patient's white blood cells are separated from the red blood cells and plasma by centrifugation in a device after the patient's whole blood is collected into the device. After the addition of 8-MOP, which has photoactivating properties, to the buffy coat/plasma blood fraction, the white cells are exposed to UVA light and then returned to the patient. 8-MOP conjugates and forms covalent bonds with DNA, as a result, DNA synthesis and cell division are inhibited [86,87].

In 1988, ECP was approved by the FDA for the treatment of CTCL [86,87]. Although ECP is often not recommended as a first-line therapy in patients with early-stage disease, it has been reported to be effective and safe in the treatment of early-stage disease [88]. In a single-centre

trial, 20 patients with erythrodermic MF or SS were treated with combination of ECP and some adjunctive agents such as IFN-α, narrow-band UVB, PUVA, isotretinoin, acitretin, methotrexate, prednisone, topical nitrogen mustard, TSEBT, and localized electron beam therapy for the hands and feets. The ORR, CRR and partial response rate were reported as 65%, 30%, and 35%, respectively [89].

Histone Deacetylase Inhibitors

Histone deacetylases (HDACs) are a class of enzymes that catalyze the removal of acetyl functional groups both from histones and from a variety of nucleic and cytoplasmic proteins [90].

Vorinostat (suberoylanilide hydroxamic or SAHA), an oral, class I/II HDAC inhibitor, is currently indicated in the treatment of patients with CTCL who have progressive, persistent, or recurrent disease during or after treatment with at least two systemic therapies [91,92]. The mechanisms of action of vorinostat include induction of differentiation, growth arrest of cancer cells and induction of apoptosis of malignant T cells [93]. It also downregulates expression of IL-10 of CTCL cells [93,94]. It was approved by the FDA in 2006. Among the HDAC inhibitors, it was the first FDA-approved agent for the treatment of relapsed/refractory CTCL [93]. Although the recommended dose is 400mg once per day, the dose may be reduced 300mg once daily in patients who cannot tolerate [91]. In a phase IIb multicenter trial, vorinostat was found

to be effective in patients with persistent, progressive, or treatment refractory cutaneous MF/SS who had received at least two prior systemic therapies at least one of which included bexarotene. Seventy-four patients with stage IB-IVA MF/SS enrolled in this study were treated with 400 mg of oral vorinostat. The ORR was 29.7% and 29.5% in stage IIB or higher patients, respectively. Reported adverse events were diarrhea, fatigue, nausea, anorexia, pulmonary embolism, and thrombocytopenia [95].

Romidepsin, which has anticancer effects, is a structurally unique, potent, bicyclic class 1 selective HDAC inhibitor. FDA approved this drug for the treatment of CTCL in patients who have received at least 1 prior systemic therapy and for the treatment of patients with peripheral T-cell lymphoma (PTCL) who have received at least 1 prior therapy [96]. In a phase I/II multicentre study, 40 patients with PTCL were treated with 14mg/m^2 romidepsin. *Maruyama* et al. reported that ORR was 43% with a complete response rate of 25%. Hematological adverse events such as lymphopenia, neutropenia, leukopenia, and thrombocytopenia were reported as side effects that require treatment [97]. *Foss* et al. reported that the objective response rates to romidepsin were 45% and 60% in patients with tumor stage and folliculotropic MF, respectively [98].

Belinostat is a HDAC inhibitor with a sulfonamide-hydroxamide structure. It is associated with high affinity for the class I, II and IV HDACs. The several mechanisms

of action of belinostat were shown in vitro. It causes accumulation of acetylated histones, restores expression of epigenetically silenced tumor suppressor genes, represses survivin, and causes cell-cycle arrest and apoptosis of malignant cells [93]. In 2014, FDA approved belinostat for the treatment of patients with relapsed or refractory PTCL [99]. In an open-label, multicentre, phase II study, patients with PTCL or CTCL who failed ≥1 prior systemic therapy were treated with belinostat 1000mg/m^2 intravenously. Forty-percent of patients with PTCL and 55% of patients with CTCL had stage IV disease. The ORRs were 25% and 14% in patients with PTCL and CTCL, respectively. Reported treatment-related adverse events were nausea, vomiting, infusion site pain, dizziness, ventricular fibrillation, thrombocytopenia, peripheral edema, apraxia, paralytic ileus, pneumonitis, and jugular vein thrombosis [100]. Belinostat is not recommended for patients who are pregnant because of its teratogenic effect [99].

Monoclonal Antibodies

Alemtuzumab, a recombinant humanized IgG1 monoclonal antibody, cause cellular cytotoxicity and lysis by binding to the CD52 surface antigen expressed on both malignant B and T cells [9]. It is approved for B-cell chronic lymphocytic leukemia (B-CLL) and multiple sclerosis in the United States [90]. In a single-centre study, 6 patients with SS were treated with alemtuzumab subcutaneously at different dosing regimens. The ORR and CRR were

reported as 83.3% and 66.7%, respectively. Although the disease-free survival at 6 months was reported as 33.3%, this duration was observed even longer in patients undergoing allogeneic stem cell transplantation (allo-SCT) after alemtuzumab treatment [101]. Despite reporting effective results in SS, adverse effects such as severe cytopenia, immune depletion, and opportunistic infections were also reported in several retrospective and prospective studies [102].

Brentuximab vedotin is a chimeric monoclonal anti-CD30 antibody conjugated with monomethyl auristatin E that is approved in the treatment of Hodgkin lymphoma and systemic anaplastic large cell lymphoma [6,103]. CD30 is a cell surface receptor that is found on Hodgkin Reed-Sternberg cells, activated monocytes, activated B and T natural killer cells, and B- and T-cell non-Hodgkin lymphomas. This receptor is uniformly expressed in Hodgkin lymphoma and anaplastic large cell lymphoma, although variable expression is occurred in MF/SS lesions [9]. Promising results have been reported in small case series with brentuximab vedotin [104, 105]. In a recently published phase II trial, 48 patients with CD30 (+) lymphoproliferative disorders or MF received brentuximab vedotin at a dose of 1.8 mg/kg with infusion. ORR and CRR were 73% and 35%, respectively [106]. In an international, open-label, randomized, phase 3, multicentre trial, 66 of 131 patients with CTCL were treated with intravenous brentuximab vedotin 1.8 mg/kg once every 3

weeks, for up to 16 3-weeks cycles. The remaining patients were received oral methotrexate 5-50 mg once per week or oral bexarotene 300mg/m^2 once per day. At the end of the median follow-up of 22.9 months, the proportion of patients achieving an objective global response lasting at least 4 months with brentuximab vedotin group and the other physician's choice group were 56.3% and 12.5%, respectively [107]. Peripheral neuropathy was noted in approximately two thirds of patients in both trials [106,107].

Mogamulizumab (KW-0761) is a defucosylated, humanized, immunoglobulin G1 monoclonal antibody that acts by binding to CCR-4 widely expressed on Th2 cells and regulatory T cells [90,108]. CCR-4 plays an important role in skin homing. The expression of CCR-4 is increased in aggressive PTCLs, particularly adult T-cell leukemia/lymphoma and CTCLs. In Japan, mogamulizumab was approved in the treatment of patients with adult T-cell leukemia/lymphoma in 2012 and in the treatment of patients with CTCL/PTCL in 2014 [102].

Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) is an infusion of multipotent stem cells derived from the bone marrow, peripheral blood, and umbilical cord into a patient for the treatment of hematologic disorders and malignancies. These stem cells can be derived in two ways: from the patient's own hematopoietic system (known as autologous) or from an HLA-matched donor who can be

a sibling (related) or a matched unrelated donor (known as allogeneic). Conditioning regimen is performed before stem cell infusion. The most common causes of transplant-morbidity and mortality are graft-versus-host disease (GVHD) and infections. Although complete remission may occur after autologous stem cell transplantation (ASCT), high relapse rates have been reported. Allo-SCT is the only potentially curative treatment option in CTCL [109].

In a recently published retrospective trial, 2 of 5 patients with CTCL who responded well to chemotherapy treated with ASCT and the remaining 3 patients with MF or SS treated with allo-SCT. Although the one of the patients died after the ASCT, partial remission was seen in the other patient treated with ASCT. In patients treated with allo-SCT, complete remission and death were reported in 2 patients and 1 patient, respectively [110]. In 8 patients (5 MF cases and 3 SS cases) who did not respond to prior treatments, the ORR was 25% after allo-SCT. Progression or relapse of the disease was noted in 38% of patients after allo-SCT. Although allo-SCT has low ORR, this treatment may be a reasonable choice for patients with refractory to prior treatment modalities [111].

Other Treatments

Quisinostat is a second-generation, pan-HDAC inhibitor that is more superior based on the tissue distribution properties and anti-proliferative activity in the nanomo-

lar range in tumor cell lines than vorinostat and panobinostat. In one phase II multicentre trial, global response rate and overall cutaneous response rate were reported 8% and 24%, respectively. The most common adverse events were nausea, diarrhea, asthenia, hypertension, thrombocytopenia and vomiting [112].

Resiquimod is one of the imidazoquinolines that effects through TLR-7 and TLR-8. By binding to these receptors, it stimulates the plasmocytoid and myeloid-derived dendritic cells involved in the innate immune system [6]. Thus, it causes an enhancement of production of cytokines such as IFN-α, IFN-γ, and IL-12 [103]. It is more potent topical agent compared to imiquimod [6]. In a phase I trial involved 12 patients with stage IA-IIA CTCL, the treated lesions had significantly improved with 0.03% and 0.06% resiquimod gel in 75% of patients. Two of 12 treated patients had complete clinical response and 9 patients had 50% or more improvement of skin disease. After topical resiquimod treatment, there may be an increase in the activation of circulating dendritic cells, which may lead to the regression of untreated lesions [113].

Conclusion

Although there are a number of alternative treatment options, there is no curative treatment for CTCLs. The stage of the disease and the prior treatments that the patient received are very important in the choice of treatment. In early-stage CTCLs, skin-directed therapies are widely used with or without systemic therapies. Indolent

course usually occurs in these patients, however, it should be remembered that the disease might develop progression or large cell transformation. In advanced-stage disease or refractory cases, systemic therapies are necessary, but patients should be closely monitored for adverse effects. Although satisfactory results have been reported, new treatment alternatives seem to be needed.

References

1. Bagherani N, Smoller BR. An overview of cutaneous T cell lymphomas. F1000Res. 2016; 5: F1000 Faculty Rev-1882.
2. Rubio-Gonzalez B, Zain J, Rosen ST, Querfeld C. Clinical manifestations and pathogenesis of cutaneous lymphomas: current status and future directions. Br J Haematol. 2017; 176: 16-36.
3. Bradfort PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood. 2009; 113: 5064-5073.
4. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005; 105: 3768-3785.
5. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016; 127: 2375-2390.

6. Berg S, Villasenor-Park J, Haun P, Kim EJ. Multidisciplinary Management of Mycosis Fungoides/ Sézary Syndrome. CurrHematolMalig Rep. 2017; 12: 234-243.

7. Junkins-Hopkins Md JM. Aggressive cutaneous T-cell lymphomas. SeminDiagnPathol. 2017; 34: 44-59.

8. Whittaker S, Hoppe R, Prince HM. How I treat mycosis fungoides and Sézary syndrome. Blood. 2016; 127: 3142-3153.

9. Devata S, Wilcox RA. Cutaneous T-Cell Lymphoma: A Review with a Focus on Targeted Agents. Am J Clin Dermatol. 2016; 17: 225-237.

10. Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/ Sézary syndrome - Update 2017. Eur J Cancer. 2017; 77: 57-74.

11. Nguyen CV, Bohjanen KA. Skin-Directed Therapies in Cutaneous T-Cell Lymphoma. Dermatol Clin. 2015; 33: 683-696.

12. Raychaudhury T. Management Strategies for Mycosis Fungoides in India. Indian J Dermatol. 2017; 62: 137-141.

13. Zackheim HS, Kashani-Sabet M, Amin S. Topical corticosteroids for mycosis fungoides. Experience in 79 patients. Arch Dermatol. 1998; 134: 949-954.

14. Liu DY, Shaath T, Rajpara AN, Hanson C, Fraga G, et al. Safe and efficacious use of intralesional steroids for the treatment of focally resistant mycosis fungoides. J Drugs Dermatol. 2015; 14: 466-471.

15. Benjamin Chase A, Markel K, Tawa MC. Optimizing Care and Compliance for the Treatment of Mycosis Fungoides Cutaneous T-Cell Lymphoma With Mechlorethamine Gel. Clin J OncolNurs. 2015; 19: E131-139.

16. Knobler E. Current management strategies for cutaneous T-cell lymphoma. Clin Dermatol. 2004; 22: 197-208.

17. McCann SA, Chase AB, Tawa MC. Gelling Your Dermatology Nursing Practice: A Practical Guide for Managing the Treatment of Mycosis Fungoides Cutaneous T-Cell Lymphoma With Mechlorethamine Gel. J Dermatol Nurses Assoc. 2016; 8: 180-192.

18. Lessin SR, Duvic M, Guitart J, Pandya AG, Strober BE, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0. 02%, gel in mycosis fungoides. JAMA Dermatol. 2013; 149: 25-32.

19. MacArthur KM, Jariwala N, Kim EJ, Rook AH. Topical Carmustine as Monotherapy or as Multimodality Therapy for Folliculotropic Mycosis

Fungoides. ActaDermVenereol. 2017; 97: 373-374.

20. Breneman D, Duvic M, Kuzel T, Yocum R, Truglia J, et al. Phase 1 and 2 trial of bexarotene gel for skin-directed treatment of patients with cutaneous T-cell lymphoma. Arch Dermatol. 2002; 138: 325-332.

21. Farkas A, Kemeny L, French LE, Dummer R. New and experimental skin-directed therapies for cutaneous lymphomas. Skin Pharmacol Physiol. 2009; 22: 322-334.

22. Besner Morin C, Roberge D, Turchin I, Petrogiannis-Haliotis T, Popradi G, et al. Tazarotene 0. 1% Cream as Monotherapy for Early-Stage Cutaneous T-Cell Lymphoma. J Cutan Med Surg. 2016; 20: 244-248.

23. Apisarnthanarax N, Talpur R, Ward S, Ni X, Kim HW, et al. Tazarotene 0. 1% gel for refractory mycosis fungoides lesions: an open-label pilot study. J Am AcadDermatol. 2004; 50: 600-607.

24. Bassiri-Tehrani S, BA BA, Cohen DE. Treatment of cutaneous T-cell lymphoma with alitretinoin gel. Int J Dermatol. 2002; 41: 104-106.

25. Trautinger F. Phototherapy of mycosis fungoides. PhotodermatolPhotoimmunolPhotomed. 2011; 27: 68-74.

26. Hodak E, Pavlovsky L. Phototherapy of Mycosis Fungoides. Dermatol Clin. 2015; 33: 697-702.

27. Olsen EA, Hodak E, Anderson T, Carter JB, Henderson M, et al. Guidelines for phototherapy of mycosis fungoides and Sézary syndrome: A consensus statement of the United States Cutaneous Lymphoma Consortium. J Am AcadDermatol. 2016; 74: 27-58.

28. Ahmad K, Rogers S, McNicholas PD, Collins P. Narrowband UVB and PUVA in the treatment of mycosis fungoides: a retrospective study. ActaDermVenereol. 2007; 87: 413-417.

29. Reidel U, Bechstein S, Lange-Asschenfeldt B, Beyer M, Vandersee S. Treatment of localized mycosis fungoides with digital UV photochemotherapy. PhotodermatolPhotoimmunolPhotomed. 2015; 31: 333-340.

30. Pavlotsky F, Hodak E, Ben Amitay D, Barzilai A. Role of bath psoralen plus ultraviolet A in early-stage mycosis fungoides. J Am AcadDermatol. 2014; 71: 536-541.

31. Ponte P, Serrão V, Apetato M. Efficacy of narrowband UVB vs. PUVA in patients with early-stage mycosis fungoides. J EurAcadDermatolVenereol. 2010; 24: 716-721.

32. Koh MJ, Chong WS. Narrow-band ultraviolet B phototherapy for mycosis fungoides in children. ClinExpDermatol. 2014; 39: 474-478.

33. Xue J, Liu C, Liu Y. Photodynamic therapy as an alternative treatment for relapsed or refractory mycosis fungoides: A systemic review. PhotodiagnosisPhotodynTher. 2017; 17: 87-91.

34. Cornejo CM, Novoa RA, Krisch RE, Kim EJ. Low-dose radiotherapy for primary cutaneous anaplastic large-cell lymphoma while on low-dose methotrexate. Cutis. 2016; 98: 253-256.

35. Han D, Xue J, Wang T, Liu Y. Observation of clinical efficacy of photodynamic therapy in 3 patients with refractory plaque-stage mycosis fungoides. PhotodiagnosisPhotodynTher. 2016; 16: 9-11.

36. Tandberg DJ, Craciunescu O, Kelsey CR. Radiation Therapy for Cutaneous T-Cell Lymphomas. Dermatol Clin. 2015; 33: 703-713.

37. Chowdhary M, Chhabra AM, Kharod S, Marwaha G. Total Skin Electron Beam Therapy in the Treatment of Mycosis Fungoides: A Review of Conventional and Low-Dose Regimens. Clin Lymphoma Myeloma Leuk. 2016; 16: 662-671.

38. Million L, Yi EJ, Wu F, Von Eyben R, Campbell BA, et al. Radiation Therapy for Primary Cutaneous Anaplastic Large Cell Lymphoma: An International Lymphoma Radiation Oncology Group Multi-institutional Experience. Int J RadiatOncolBiol Phys. 2016; 95: 1454-1459.

39. Topal IO, Goncu EK, Ozekinci S, Ayaz G, Aksaray F. Primary cutaneous CD4(+) small/medium-sized T-cell lymphoma of the face: successful treatment with radiation therapy. J DtschDermatolGes. 2016; 14: 522-524.

40. Danish HH, Heumann TR, Bradley KT, Switchenko J, Esiashvili N, et al. CD30+ Cutaneous T Cell Lymphoma: Response to Rotational Total Skin Electron Irradiation. Dermatol Ther (Heidelb). 2016; 6: 251-263.

41. Elsayad K, Kriz J, Moustakis C, Scobioala S, Reinartz G, et al. Total Skin Electron Beam for Primary Cutaneous T-cell Lymphoma. Int J RadiatOncolBiol Phys. 2015; 93: 1077-1086.

42. Akilov OE, Grant C, Frye R, Bates S, Piekarz R, et al. Low-dose electron beam radiation and romidepsin therapy for symptomatic cutaneous T-cell lymphoma lesions. Br J Dermatol. 2012; 167: 194-197.

43. Lindahl LM, Kamstrup MR, Petersen PM, Wirén J, Fenger-Grøn M, et al. Total skin electron beam therapy for cutaneous T-cell lymphoma: a nationwide cohort study from Denmark. Acta Oncol. 2011; 50: 1199-1205.

44. Conill C, Navalpotro B, López I, Estrach T. Results of radiotherapy in primary cutaneous lymphoma. ClinTranslOncol. 2006; 8: 430-434.

45. Elsayad K, Susek KH, Eich HT. Total Skin Electron Beam Therapy as Part of Multimodal Treatment Strategies for Primary Cutaneous T-Cell Lymphoma. Oncol Res Treat. 2017; 40: 244-252.

46. Shipman AR, Scarisbrick J. New Treatment Options for Mycosis Fungoides. Indian J Dermatol. 2016; 61: 119.

47. Lewis DJ, Byekova YA, Emge DA, Duvic M. Complete resolution of mycosis fungoides tumors with imiquimod 5% cream: a case series. J Dermatolog Treat. 2017: 1-3.

48. Huen AO, Kim EJ. The Role of Systemic Retinoids in the Treatment of Cutaneous T-Cell Lymphoma. DermatolClin. 2015; 33: 715-729.

49. Kessler JF, Meyskens FL Jr, Levine N, Lynch PJ, Jones SE. Treatment of cutaneous T-cell lymphoma (mycosis fungoides) with 13-cis-retinoic acid. Lancet. 1983; 1: 1345-1347.

50. Leverkus M, Rose C, Bröcker EB, Goebeler M. Follicular cutaneous T-cell lymphoma: beneficial effect of isotretinoin for persisting cysts and comedones. Br J Dermatol. 2005; 152: 193-194.

51. Cheeley J, Sahn RE, DeLong LK, Parker SR. Acitretin for the treatment of cutaneous T-cell lymphoma. J Am AcadDermatol. 2013; 68: 247-254.

52. Hamada T, Sugaya M, Tokura Y, Ohtsuka M, Tsuboi R, et al. Phase I/II study of the oral retinoid

X receptor agonist bexarotene in Japanese patients with cutaneous T-cell lymphomas. J Dermatol. 2017; 44: 135-142.

53. Rupoli S, Canafoglia L, Goteri G, Leoni P, Brandozzi G, et al. Results of a prospective phase II trial with oral low-dose bexarotene plus photochemotherapy (PUVA) in refractory and/or relapsed patients with mycosis fungoides. Eur J Dermatol. 2016; 26: 13-20.

54. Scarisbrick JJ, Morris S, Azurdia R, Illidge T, Parry E, et al. U. K. consensus statement on safe clinical prescribing of bexarotene for patients with cutaneous T-cell lymphoma. Br J Dermatol. 2013; 168: 192-200.

55. Gniadecki R, Assaf C, Bagot M, Dummer R, Duvic M, et al. The optimal use of bexarotene in cutaneous T-cell lymphoma. Br J Dermatol. 2007; 157: 433-440.

56. Eshagh K, Romero LS, So JK, Zhao XF. Late-onset bexarotene-induced CD4 lymphopenia in a cutaneous T-cell lymphoma patient. Cutis. 2017; 99: E30-E34.

57. Coors EA, von den Driesch P. Treatment of 2 patients with mycosis fungoides with alitretinoin. J Am AcadDermatol. 2012; 67: e265-267.

58. Schmitz L, Bierhoff E, Dirschka T. Alitretinoin: an effective treatment option for pagetoid reticulosis. J DtschDermatolGes. 2013; 11: 1194-1195.

59. Miernik B, Schmidt V, Technau-Hafsi K, Kern JS, Meiss F. Alitretinoin in the treatment of palmoplantar mycosis fungoides: a new and promising therapeutic approach. ClinExpDermatol. 2015; 40: 445-447.

60. Park J, Kwon O, Park K, Chung H. Alitretinoin treatment in mycosis fungoides with CD30-positive large cell transformation. ClinExpDermatol. 2017; 42: 341-342.

61. Kapser C, Herzinger T, Ruzicka T, Flaig M, Molin S. Treatment of cutaneous T-cell lymphoma with oral alitretinoin. J EurAcadDermatolVenereol. 2015; 29: 783-788.

62. Zhang H, Gupta R, Wang JC, Lipton JF, Huang YW. Subcutaneous panniculitis-like T-cell lymphoma in a patient with long-term remission with standard chemotherapy. J Natl Med Assoc. 2007; 99: 1190-1192.

63. Mebazaa A, Dupuy A, Rybojad M, Mouly F, Moulonguet I, et al. ESHAP for primary cutaneous T-cell lymphomas: efficacy and tolerance in 11 patients. Hematol J. 2005; 5: 553-538.

64. Luo Y, Zhang LI, Sun YJ, DU H, Yang GL. Syringotropic mycosis fungoides responding well to VELP chemotherapy: A case report. ExpTher Med. 2016; 11: 2254-2258.

65. Tian C, Yu Y, Zhang Y. A case report of primary cutaneous natural killer/T-cell lymphoma. Mol-ClinOncol. 2016; 5: 777-778.

66. Dummer R, Quaglino P, Becker JC, Hasan B, Karrasch M, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin mono chemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. J ClinOncol. 2012; 30: 4091-4097.

67. Buhl T, Bertsch HP, Kaune KM, Mitteldorf C, Schön MP, et al. Low-dose gemcitabine efficacious in three patients with tumor-stage mycosis fungoides. Clin Lymphoma Myeloma. 2009; 9: E21-24.

68. Duvic M. Choosing a systemic treatment for advanced stage cutaneous T-cell lymphoma: mycosis fungoides and Sézary syndrome. Hematology Am SocHematolEduc Program. 2015; 2015: 529-544.

69. Chung CG, Poligone B. Other Chemotherapeutic Agents in Cutaneous T-Cell Lymphoma. Dermatol Clin. 2015; 33: 787-805.

70. Wollina U, Langner D, Hansel G, Haroske G. Pegylated liposomal-encapsulated doxorubicin in cutaneous composite lymphoma: A case report. Medicine (Baltimore). 2016; 95: e4796.

71. Illidge T, Chan C, Counsell N, Morris S, Scarisbrick J, et al. Phase II study of gemcitabine and bexarotene (GEMBEX) in the treatment of cutaneous T-cell lymphoma. Br J Cancer. 2013; 109: 2566-2573.

72. West ES, Shinkai K, Ai WZ, Pincus LB. Remission of subcutaneous panniculitis-like T-cell lymphoma in a pregnant woman after treatment with oral corticosteroids as monotherapy. JAAD Case Rep. 2017; 3: 87-89.

73. Asati DP, Ingle V, Joshi D, Tiwari A. Subcutaneous panniculitis-like T-cell lymphoma with macrophage activation syndrome treated by cyclosporine and prednisolone. Indian Dermatol Online J. 2016; 7: 529-532.

74. Guenova E, Schanz S, Hoetzenecker W, DeSimone JA, Mehra T, et al. Systemic corticosteroids for subcutaneous panniculitis-like T-cell lymphoma. Br J Dermatol. 2014; 171: 891-894.

75. Spaccarelli N, Rook AH. The Use of Interferons in the Treatment of Cutaneous T-Cell Lymphoma. Dermatol Clin. 2015; 33: 731-745.

76. Bunn PA Jr, Foon KA, Ihde DC, Longo DL, Eddy J, et al. Recombinant leukocyte A interferon: an active agent in advanced cutaneous T-cell lymphomas. Ann Intern Med. 1984; 101: 484-487.

77. Papa G, Tura S, Mandelli F, Vegna ML, Defazio D, et al. Is interferon alpha in cutaneous T-cell lymphoma a treatment of choice?Br J Haematol. 1991; 79: 48-51.

78. Chiarion-Sileni V, Bononi A, Fornasa CV, Soraru M, Alaibac M, et al. Phase II trial of interferon-alpha-2a plus psolaren with ultraviolet light A in patients with cutaneous T-cell lymphoma. Cancer. 2002; 95: 569-575.

79. Stadler R, Otte HG, Luger T, Henz BM, Kühl P, et al. Prospective randomized multicenter clinical trial on the use of interferon -2a plus acitretin versus interferon -2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. Blood. 1998; 92: 3578-3581.

80. Rupoli S, Goteri G, Pulini S, Filosa A, Tassetti A, et al. Long-term experience with low-dose interferon-alpha and PUVA in the management of early mycosis fungoides. Eur J Haematol. 2005; 75: 136-145.

81. Nikolaou V, Siakantaris MP, Vassilakopoulos TP, Papadavid E, Stratigos A, et al. PUVA plus interferon α2b in the treatment of advanced or refractory to PUVA early stage mycosis fungoides: a case series. J EurAcadDermatolVenereol. 2011; 25: 354-357.

82. Wozniak MB, Tracey L, Ortiz-Romero PL, Montes S, Alvarez M, et al. Psoralen plus ultraviolet A +/- interferon-alpha treatment resistance in mycosis fungoides: the role of tumour microenvironment, nuclear transcription factor-kappaB and T-cell receptor pathways. Br J Dermatol. 2009; 160: 92-102.

83. Hüsken AC, Tsianakas A, Hensen P, Nashan D, Loquai C, et al. Comparison of pegylated interferon α-2b plus psoralen PUVA versus standard interferon α-2a plus PUVA in patients with cutaneous T-cell lymphoma. J EurAcadDermatolVenereol. 2012; 26: 71-78.

84. Wagner AE, Wada D, Bowen G, Gaffney DK. Mycosis fungoides: the addition of concurrent and adjuvant interferon to total skin electron beam therapy. Br J Dermatol. 2013; 169: 715-718.

85. Samimi S, Morrissey K, Anshelevich S, Evans K, Gardner J, et al. Romidepsin and interferon gamma: a novel combination for refractory cutaneous T-cell lymphoma. J Am AcadDermatol. 2013; 68: e5-6.

86. Zic JA. Extracorporeal Photopheresis in the Treatment of Mycosis Fungoides and Sézary Syndrome. Dermatol Clin. 2015; 33: 765-776.

87. Knobler R, Berlin G, Calzavara-Pinton P, Greinix H, Jaksch P, et al. Guidelines on the use of extra-

corporeal photopheresis. J EurAcadDermatolVenereol. 2014; 28: 1-37.

88. Lewis DJ, Duvic M. Extracorporeal photopheresis for the treatment of early-stage mycosis fungoides. Dermatol Ther. 2017; 30.

89. Atzmony L, Amitay-Laish I, Gurion R, Shahal-Zimra Y, Hodak E. Erythrodermic mycosis fungoides and Sézary syndrome treated with extracorporeal photopheresis as part of a multimodality regimen: A single-centre experience. J EurAcadDermatolVenereol. 2015; 29: 2382-2389.

90. Leuchte K, Schlaak M, Stadler R, Theurich S, von Bergwelt-Baildon M. Innovative Treatment Concepts for Cutaneous T-Cell Lymphoma Based on Microenvironment Modulation. Oncol Res Treat. 2017; 40: 262-269.

91. Abraham J, Stenger M, Rhee J. Vorinostat in cutaneous T-cell lymphoma. CommunOncol. 2007; 4: 384-386.

92. Duvic M, Vu J. Update on the treatment of cutaneous T-cell lymphoma (CTCL): Focus on vorinostat. Biologics. 2007; 1: 377-392.

93. Duvic M. Histone Deacetylase Inhibitors for Cutaneous T-Cell Lymphoma. Dermatol Clin. 2015; 33: 757-764.

94. Tiffon C, Adams J, van der Fits L, Wen S, Townsend P, 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: 1590-1602.

95. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, 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.

96. Reddy SA. Romidepsin for the treatment of relapsed/refractory cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome): Use in a community setting. Crit Rev Oncol Hematol. 2016; 106: 99-107.

97. Maruyama D, Tobinai K, Ogura M, Uchida T, Hatake K, et al. Romidepsin in Japanese patients with relapsed or refractory peripheral T-cell lymphoma: a phase I/II and pharmacokinetics study. Int J Hematol. 2017.

98. Foss F, Duvic M, Lerner A, Waksman J, Whittaker S. Clinical Efficacy of Romidepsin in Tumor Stage and Folliculotropic Mycosis Fungoides. Clin Lymphoma Myeloma Leuk. 2016; 16: 637-643.

99. Sawas A, Radeski D, O'Connor OA. Belinostat in patients with refractory or relapsed peripheral T-

cell lymphoma: a perspective review. TherAdvHematol. 2015; 6: 202-208.

100. Foss F, Advani R, Duvic M, Hymes KB, Intragumtornchai T, et al. A Phase II trial of Belinostat (PXD101) in patients with relapsed or refractory peripheral or cutaneous T-cell lymphoma. Br J Haematol. 2015; 168: 811-819.

101. Novelli S, García-Muret P, Sierra J, Briones J. Alemtuzumab treatment for Sézary syndrome: A single-center experience. J Dermatolog Treat. 2016; 27: 179-181.

102. Bagot M. New Targeted Treatments for Cutaneous T-cell Lymphomas. Indian J Dermatol. 2017; 62: 142-145.

103. Rozati S, Kim YH. Experimental treatment strategies in primary cutaneous T-cell lymphomas. CurrOpinOncol. 2016; 28: 166-171.

104. Mehra T, Ikenberg K, Moos RM, Benz R, Nair G, et al. Brentuximab as a treatment for CD30+ mycosis fungoides and Sézary syndrome. JAMA Dermatol. 2015; 151: 73-77.

105. Broccoli A, Derenzini E, Pellegrini C, Narducci R, Stefani G, et al. Complete response of relapsed systemic and cutaneous anaplastic large cell lymphoma using brentuximab vedotin: 2 case reports. Lymphoma Myeloma Leuk. 2013; 13: 493-495.

106. Duvic M, Tetzlaff MT, Gangar P, Clos AL, Sui D, et al. Results of a Phase II Trial of Brentuximab Vedotin for CD30+ Cutaneous T-Cell Lymphoma and LymphomatoidPapulosis. J Clin Oncol. 2015; 33: 3759-3765.

107. Prince HM, Kim YH, Horwitz SM, Dummer R, Scarisbrick J, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet. 2017; 390: 555-566.

108. Duvic M, Evans M, Wang C. Mogamulizumab for the treatment of cutaneous T-cell lymphoma: recent advances and clinical potential. TherAdvHematol. 2016; 7: 171-174.

109. Virmani P, Zain J, Rosen ST, Myskowski PL, Querfeld C. Hematopoietic Stem Cell Transplant for Mycosis Fungoides and Sézary Syndrome. Dermatol Clin. 2015; 33: 807-818.

110. Saruta H, Ohata C, Muto I, Imamura T, Oku E, et al. Hematopoietic stem cell transplantation in advanced cutaneous T-cell lymphoma. J Dermatol. 2017.

111. Atilla E, Atilla PA, Bozdag SC, Yuksel MK, Toprak SK, et al. Allogeneic hematopoietic stem cell transplantation for refractory mycosis fungoides (MF) and Sezary syndrome (SS). Int J Hematol. 2017.

112. Child F, Ortiz-Romero PL, Alvarez R, Bagot M, Stadler R, et al. Phase II multicentre trial of oral quisinostat, a histone deacetylase inhibitor, in patients with previously treated stage IB-IVA mycosis fungoides/Sézary syndrome. Br J Dermatol. 2016; 175: 80-88.

113. Rook AH, Gelfand JM, Wysocka M, Troxel AB, Benoit B, et al. Topical resiquimod can induce disease regression and enhance T-cell effector functions in cutaneous T-cell lymphoma. Blood. 2015; 126: 1452-1461.