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EDITORIAL

Mycosis fungoides and Sézary syndrome: Role of chemokines and chemokine receptors

Stephen Chu-Sung Hu

Stephen Chu-Sung Hu, Department of Dermatology, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan
Stephen Chu-Sung Hu, Department of Dermatology, College of Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan
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Correspondence to: Stephen Chu-Sung Hu, MBBS, M.Phil, Department of Dermatology, Kaohsiung Medical University Hospital, No. 100, Tzyou 1st Road, Kaohsiung 807, Taiwan. stephenhu30@hotmail.com
Telephone: +886-7-3121101
Fax: +886-7-3118894
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Abstract

Mycosis fungoides is the most common form of cutaneous T-cell lymphoma (CTCL), and is characterized by a clonal expansion of malignant $CD4^+$ T lymphocytes with skin-homing properties. Clinically and pathologically, mycosis fungoides can be categorized into patch, plaque and tumor stages. The clinical course of mycosis fungoides is usually chronic and indolent, but a proportion of patients may develop progressive disease with peripheral blood, lymph node and visceral organ involvement. Sézary syndrome is an aggressive leukemic form of CTCL characterized by a clonal population of malignant T cells in the peripheral blood. Various forms of skin-directed and systemic treatments are available for mycosis fungoides and Sézary syndrome. However, current treatments are generally not curative, and can only control the disease. Currently, the etiology and pathogenesis of mycosis fungoides and Sézary syndrome are not well defined. Proposed mechanisms include chronic antigenic stimulation by infectious agents, expression of specific adhesion molecules, altered cytokine production, mutations of oncogenes and tumor suppressor genes, and avoidance of apoptosis. In recent years, a number of chemokine receptors and their corresponding chemokine ligands have been found to contribute to the migration and survival of lymphoma cells in mycosis fungoides and Sézary syndrome, including CC chemokine receptor 4 (CCR4), CCR10, C-X-C chemokine receptor type 4 (CXCR4), CCR7, CCR3 and CXCR3. Since chemokines and chemokine receptors have been found to play important roles in the pathophysiology of mycosis fungoides and Sézary syndrome, they may be potentially useful targets for the development of new treatments for these diseases in the future.

Key words: Mycosis fungoides; Sézary syndrome; Skin-homing; Chemokines; Chemokine receptors

Core tip: Mycosis fungoides and Sézary syndrome are characterized by a clonal expansion of malignant $CD4^+$ T lymphocytes with skin-homing properties. Currently, treatment options for mycosis fungoides and Sézary syndrome are limited. The lack of effective targeted therapy results in part from the poor understanding regarding the pathophysiology of these diseases. Recently, a number of chemokines and chemokine receptors have been found to contribute to the pathogenesis of mycosis fungoides and Sézary syndrome, including the

CC chemokine receptor 4 (CCR4)/chemokine (C-C motif) ligand 17 (CCL17), CCR10/CCL27, C-X-C chemokine receptor type 4/chemokine (C-X-C Motif) ligand 12 and CCR7/CCL21 axes. Therefore, these chemokines and chemokine receptors may be potentially useful targets for the treatment of these lymphomas in the future.

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INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) is a group of diseases characterized by malignant T lymphocytes infiltrating the skin, and includes mycosis fungoides, Sézary syndrome, lymphomatoid papulosis, anaplastic large cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, cutaneous natural killer/T-cell lymphoma, and primary cutaneous peripheral T-cell lymphoma[1]. This Editorial focuses on mycosis fungoides and Sézary syndrome.

Mycosis fungoides is the most common form of CTCL, and is characterized by a clonal expansion of malignant $CD4^+$ T lymphocytes with skin-homing properties[2]. It is more common in the middle-aged and elderly, and is about twice more common in males than females[3]. However, mycosis fungoides can also occur in children and young adults[4]. Clinically and pathologically, mycosis fungoides can be categorized into patch, plaque and tumor stages. The clinical course of mycosis fungoides is usually chronic and indolent, but a subset of patients may develop progressive disease with peripheral blood, lymph node and visceral organ involvement[5]. Patients with mycosis fungoides also have a higher risk of developing a second malignancy, especially other types of lymphomas[6,7].

Sézary syndrome is an aggressive leukemic form of CTCL showing a clonal population of malignant T cells in the peripheral blood. Traditionally, mycosis fungoides and Sézary syndrome have been regarded as a spectrum of diseases with a common pathogenesis. More recently, investigations have indicated that mycosis fungoides and Sézary syndrome are two different diseases which originate from distinct T-cell subsets[8]. Mycosis fungoides is believed to be a lymphoma arising from skin resident "effector" memory T cells, in which atypical lymphocytes remain confined to the skin. On the other hand, Sézary syndrome is regarded as a lymphoma of "central" memory T cells, in which atypical lymphocytes circulate between the blood, skin and lymph nodes. This may partially account for the differences in biologic behaviors and prognosis between these two diseases.

CLINICAL FEATURES

Classically, mycosis fungoides presents as erythematous patches and plaques, often associated with scaling (Figure 1). The skin lesions are usually located on non-sun exposed areas, such as the chest, abdomen, back, buttocks, groin and thigh. However, any region of the body can be affected. Pruritus is a common symptom. The skin lesions have usually been present for months to years, and they may gradually become thicker and develop into tumors. The three different types of skin lesions (patches, plaques, tumors) can sometimes be seen in a single patient concurrently. In certain patients, mycosis fungoides may progress into an erythrodermic form with generalized erythema and scaling of the skin[5].

Sézary syndrome is an aggressive leukemic form of CTCL. It is characterized by erythroderma (generalized erythema and scaling of the skin involving more than 80% of the body surface area), and a clonal population of malignant T lymphocytes in the peripheral blood[9,10]. Lymphadenopathy may or may not be present. This disease usually develops de novo without preceding mycosis fungoides.

HISTOPATHOLOGY AND IMMUNOPHENOTYPE

On histopathological examination, skin lesions of mycosis fungoides are characterized by atypical lymphocytes infiltrating mainly the dermis (Figure 2). The atypical lymphocytes are usually hyperchromatic, may have a haloed appearance, and show irregular, convoluted, or cerebriform nuclei[11]. They often accumulate in a band-like distribution at the dermoepidermal junction. They show a tendency for epidermotropism (migration into the epidermis without epidermal spongiosis), and may form aggregates with Langerhans cells in the epidermis (Pautrier's microabscess)[12]. There may be an accompanying infiltrate of reactive inflammatory cells.

On immunohistochemical staining, the atypical lymphocytes in mycosis fungoides are usually $CD4^+$, and there is an elevated CD4:CD8 ratio[11,13]. However, in a minority of cases the atypical lymphocytes are $CD8^+$[14]. The atypical cells are also $CD45RO^+$, which is a marker of memory T cells[15]. In addition, there is a loss of T cell antigens (including CD2, CD5, CD7 and CD26)[15]. In Sézary syndrome and certain cases of mycosis fungoides, Sézary cells can be detected in the peripheral blood by flow cytometry, and are identified as $CD4^+CD7^-$ and/or $CD4^+CD26^-$ cells[16,17].

The skin lesions of mycosis fungoides may show a dominant T cell clone. This is demonstrated by the presence of clonal T cell receptor gene rearrangement on polymerase chain reaction (PCR) analysis of the skin[18,19]. In Sézary syndrome patients, a large clonal population of atypical T lymphocytes may be found in the peripheral blood, determined by molecular methods (T cell receptor gene rearrangements by PCR) and flow

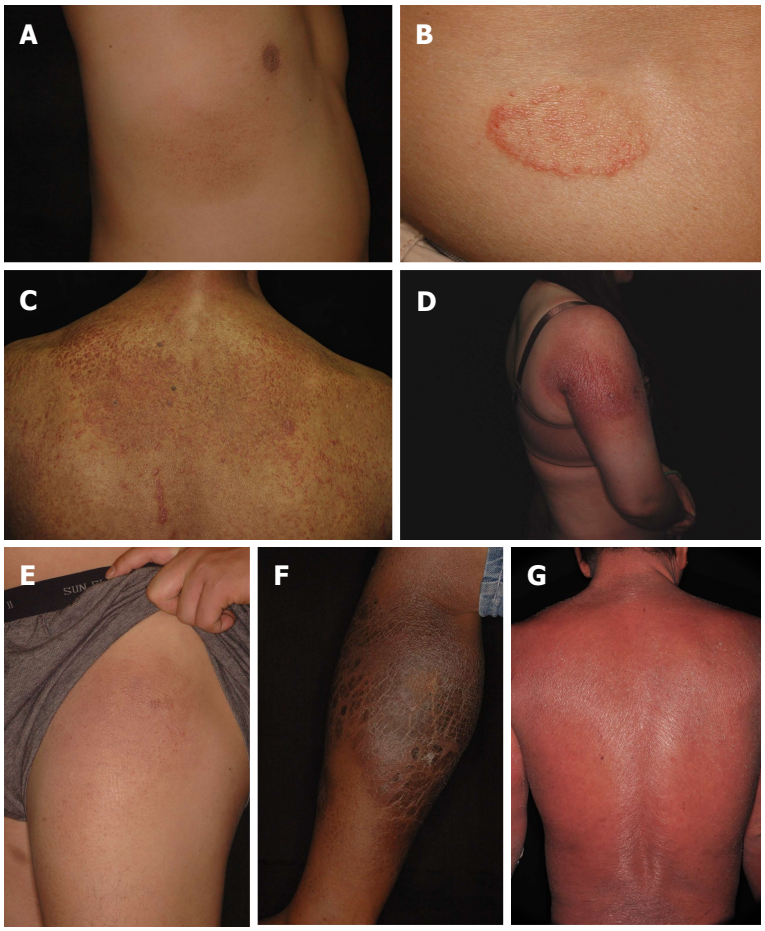

Figure 1 Clinical images showing patch stage (A), plaque stage (B-E), tumor stage (F), and erythrodermic (G) mycosis fungoides.

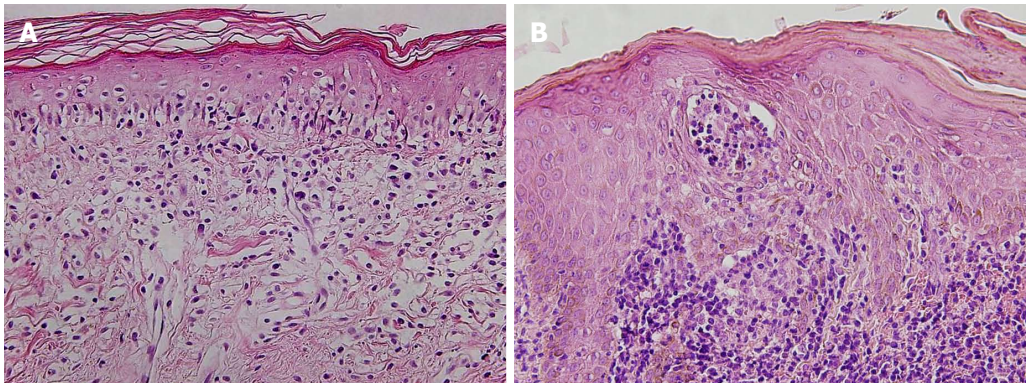

Figure 2 Pathological examination of mycosis fungoides lesions reveals atypical lymphocytes with epidermotropism (A) and formation of Pautrier's microabscess (B).

cytometry (expression of specific T cell receptor Vβ epitopes)[10,20].

EVALUATION OF PATIENTS

Patients should undergo a detailed physical examination to determine the total body surface area involved by lymphoma, as well as the surface area involved by patch, plaque and tumor stages[10]. This provides a measure of the skin tumor burden.

Laboratory tests that should be performed in patients with mycosis fungoides and Sézary syndrome include a complete blood count with differential counts, electrolytes and lactate dehydrogenase. A skin biopsy should be undertaken for histopathological examination, immunohistochemistry and T cell receptor gene rearrangement studies. Peripheral blood should be examined for Sézary cell count and clonality of circulating T cells. Computed tomography scans with positron emission tomography are useful for determining internal organ involvement[21]. Lymph node biopsy should also be performed in cases with lymphadenopathy.

STAGING AND PROGNOSIS

The staging of mycosis fungoides is based on the International Society for Cutaneous Lymphomas/European Organization for Research and Treatment of Cancer system, and takes into account the extent of skin involvement (T), lymph node disease (N), visceral involvement (M), and the presence of Sézary cells in the peripheral blood (B). The TNMB classification is converted into a clinical stage[10,22].

The prognosis in patients with early stage mycosis fungoides (stage Ⅰ A) is good, and these patients have a similar life expectancy as the general population[23]. Poor prognostic factors for mycosis fungoides include advanced stage, older age, elevated lactate dehydrogenase levels, presence of erythroderma, large cell transformation, presence of a clonal population of atypical lymphocytes in the peripheral blood, and high Sézary cell count[24-28]. The presence of $CD8^+$ T cells in the skin of mycosis fungoides patients is associated with better prognosis, since this may lead to a host anti-lymphoma response[29].

ETIOLOGY AND PATHOGENESIS

The etiology and pathogenesis of mycosis fungoides and Sézary syndrome is currently not well defined. It has been proposed that mycosis fungoides is caused by chronic antigenic stimulation, which results in lymphocyte proliferation and eventually a clonal expansion of $CD4^+$ T helper cells in the skin. Certain infections, such as Staphylococcus aureus and Chlamydia species, have been implicated in the etiology of mycosis fungoides[30-32].

Atypical lymphocytes in patients with mycosis fungoides and Sézary syndrome have been found to express the adhesion molecule cutaneous lymphocyte antigen, which may mediate the migration of lymphoma cells to the skin[33].

The cytokine profile in mycosis fungoides also changes according to the stage of the disease. In early stages of mycosis fungoides, Th1 cytokines [(interferon-γ, interleukin-12 (IL-12), IL-2] predominate[15,34]. In later stages of mycosis fungoides and Sézary syndrome, a shift from Th1 to Th2 cytokine profile is found, including IL-4, IL-5, IL-10, and IL-13[35-37].

T cell proliferation and cell cycle control may be dysregulated in patients with mycosis fungoides. Amplification and overexpression of the oncogene JUNB were found in a subset of patients with mycosis fungoides and Sézary syndrome[38]. Increased expression of the oncoproteins ras and myc has been implicated in the pathogenesis of mycosis fungoides[39].

Atypical lymphocytes in mycosis fungoides and Sézary syndrome have also been shown to be resistant to apoptosis. Fas is a death receptor which can mediate apoptosis, and studies have shown that low Fas expression and impaired Fas-mediated apoptosis may play a role in the pathogenesis of mycosis fungoides[40-42].

CHEMOKINES AND CHEMOKINE RECEPTORS IN MYCOSIS FUNGOIDES AND SÉZARY SYNDROME

Chemokines and chemokine receptors were initially found to play important roles in mediating the chemotaxis (directional migration) of leukocytes[43]. Chemokines are a family of small polypeptides, and are categorized based on the location of cysteine residues near their amino termini into four families (C, CC, CXC, and CX3C). Chemokines bind to chemokine receptors, which are seven-membrane spanning, G-protein-coupled receptors. There are more than 50 different chemokines and at least 18 different chemokine receptors identified to date[44]. There are redundancies in the binding between chemokines and chemokine receptors, as some chemokines bind to multiple chemokine receptors, and vice versa. The activation of chemokine receptors by chemokines may activate various downstream signaling pathways, including the mitogen-activated protein kinase, phosphoinositide-3 kinase, and mammalian target of rapamycin (mTOR) pathways.

In recent years, various types of cancer cells have been found to express chemokine receptors, which have been shown to play important roles in cancer growth, progression and metastasis[45]. Apart from mediating cancer cell migration, chemokine receptors have also been demonstrated to mediate cancer cell proliferation, survival/apoptosis, and angiogenesis[46,47]. A number of chemokines and chemokine receptors have been found to contribute to the migration and survival of lymphoma cells in mycosis fungoides and Sézary syndrome (Table 1)[48-50].

CHEMOKINE RECEPTOR CC CHEMOKINE RECEPTOR 4

The chemokine receptor CC chemokine receptor 4 (CCR4) has been found to be important in mediating the migration of normal lymphocytes to inflamed skin[51,52]. There are increased percentages of T lymphocytes expressing CCR4 in the blood and skin lesions of patients with CTCL (including mycosis fungoides and Sézary syndrome)[8,53-55]. CCR4 expression is also seen in mycosis fungoides tumors with large cell transformation[56]. Furthermore, CCR4 was found to be expressed by mycosis fungoides cell lines, and activation of the CCR4 receptor promoted migration of lymphoma cells[57]. The CCR4 ligand chemokine (C-C motif) ligand 17 (CCL17) (thymus and activation regulated chemokine) is produced by activated epidermal keratinocytes, dendritic cells and endothelial cells, and its expression is upregulated in the skin lesions and serum of mycosis fungoides patients[58,59]. In addition, serum CCL17 levels were found to correlate with disease activity in patients with mycosis fungoides[59].

Table 1 Role of chemokines and chemokines receptors in the pathogenesis of mycosis fungoides and Sézary syndrome[8,16,51-85]

Chemokine receptor	Chemokine	Role in pathogenesis of mycosis fungoides and Sézary syndrome
CCR4	CCL17 (TARC)	Increased percentages of T lymphocytes expressing CCR4 in the blood and skin lesions of CTCL patients
	CCL22	Activation of CCR4 promoted migration of mycosis fungoides cell lines
		CCL17 expression is upregulated in the skin lesions and serum of mycosis fungoides patients
CCR10	CCL27 (CTACK)	CCR10 is expressed by malignant lymphocytes in skin lesions and peripheral blood of patients with mycosis fungoides and Sézary syndrome
		The level of CCL27 is increased in the serum and skin of patients with mycosis fungoides
CXCR4	CXCL12 (SDF)	CXCR4 is expressed by Sézary cells, and acts as a chemotactic factor for Sézary cells
		Loss of the cell-surface antigen CD26 (which cleaves and deactivates the CXCL12) is a characteristic feature in Sézary syndrome
CCR7	CCL19 (MIP-3b)	CCR7 is expressed on atypical lymphocytes of Sézary syndrome
	CCL21 (SLC)	CCR7 promotes migration of Sézary cells
		CCR7 was expressed in mycosis fungoides skin lesions, and its expression correlated with subcutaneous extension of lymphoma cells
		Activation of CCR7 by its ligand CCL21 promotes MyLa (mycosis fungoides cell line) cell migration through the mTOR pathway
CCR3	Eotaxin-3	Skin lesions of CTCL show higher expression of CCR3 and eotaxin-3
	Eotaxin-1	CTCL patients show higher serum levels of eotaxin-3 and eotaxin-1
CXCR3	CXCL9	CXCR3 is expressed in low-grade mycosis fungoides
	CXCL10	
	CXCL11	

CCR: CC chemokine receptor; CCL: Chemokine (C-C motif) ligand; TARC: Thymus and activation regulated chemokine; CTCL: Cutaneous T-cell lymphoma; CTACK: Cutaneous T-cell attracting chemokine; CXCR4: C-X-C chemokine receptor type 4; CXCL12: Chemokine (C-X-C Motif) ligand 12; SDF: Stromal cell-derived factor; MIP: Macrophage inflammatory protein; SLC: Secondary lymphoid-tissue chemokine.

Therefore, the interaction between CCR4 and CCL17 may play a role in the homing of mycosis fungoides cells to the skin or promote the survival of lymphoma cells.

CHEMOKINE RECEPTOR CCR10

The chemokine receptor CCR10 has been found to be expressed by normal lymphocytes which home to the skin[60,61]. CCR10 has been demonstrated to be expressed by malignant lymphocytes in skin lesions of mycosis fungoides and Sézary syndrome, and mediated migration of Sézary cell line[62,63]. In patients with mycosis fungoides and Sézary syndrome, increased numbers of lymphocytes expressing CCR10 was also found in the peripheral blood[63-65]. The CCR10 ligand CCL27 (cutaneous T-cell attracting chemokine), a skin-specific chemokine, is synthesized by epidermal keratinocytes[66,67]. The level of CCL27 was increased in the serum and skin of patients with mycosis fungoides[63,68], and may act as a therapeutic marker following interferon-α and psoralen and ultraviolet-A (PUVA) treatment[69].

CHEMOKINE RECEPTOR C-X-C CHEMOKINE RECEPTOR TYPE 4

The chemokine receptor C-X-C chemokine receptor type 4 (CXCR4) may also be involved in homing of mycosis fungoides and Sézary cells to skin. CXCR4 has been demonstrated to be expressed by Sézary cells, and acts as a chemotactic factor for Sézary cells[55]. CXCR4 has also been shown to be expressed in mycosis fungoides skin lesions[70]. The ligand for CXCR4 is the chemokine chemokine (C-X-C Motif) ligand 12 (CXCL12) (also known as stromal cell-derived factor 1), which is expressed by skin dermal fibroblasts and endothelial cells[71,72]. In Sézary syndrome, loss of the cell-surface antigen CD26 is a characteristic feature[16,73]. CD26 is a dipeptidyl peptidase which cleaves and deactivates CXCL12, preventing it from activating CXCR4. The downregulation of CD26 and subsequent increased levels of CXCL12 may promote CXCL12-induced chemotaxis of Sézary cells[55].

CHEMOKINE RECEPTOR CCR7

CCR7 is a chemokine receptor which has been discovered to mediate the migration of T lymphocytes and dendritic cells to lymphatic vessels and lymph nodes[74-76]. The ligands for CCR7 are CCL19 (also known as macrophage inflammatory protein-3b, MIP-3b) and CCL21 (also known as secondary lymphoid-tissue chemokine). CCR7 has been found to be involved in the lymph node metastasis of certain cancer cells[77-79]. In addition, CCR7 plays a role in cancer cell proliferation, migration and invasion.

Previous studies have indicated that CCR7 is expressed on atypical lymphocytes of Sézary syndrome[8,64,65], and may promote migration of Sézary cells[80]. CCR7 is also expressed in tumor-stage mycosis fungoides[70]. Recently, our research group found that CCR7 was expressed in 62% (13 out of 21) of mycosis fungoides skin tissue specimens, and its expression correlated with subcutaneous extension of lymphoma cells (an indication of lesion thickness). In addition, we showed that CCR7

Table 2 Current treatment strategies for mycosis fungoides and Sézary syndrome

Skin-directed therapies	Systemic therapies
Topical corticosteroids	Oral retinoid (bexarotene)
Topical nitrogen mustard	IL-12
Topical retinoid (bexarotene)	Interferon-α
Ultraviolet light phototherapy (PUVA, narrowband UVB)	Histone deacetylase inhibitors
	Extracorporeal photopheresis
Radiation therapy	Methotrexate
	Chemotherapy
	Hematopoietic stem cell transplantation

PUVA: Psoralen and ultraviolet-A; IL-12: Interleukin 12.

expression was increased on the surface of MyLa cells (a human mycosis fungoides cell line) compared to peripheral blood mononuclear cells. Activation of CCR7 by its ligand CCL21 promoted MyLa cell migration but not proliferation. We also demonstrated that the CCL21-induced MyLa cell migration was mediated through the mTOR pathway[81].

OTHER CHEMOKINE RECEPTORS

It has been demonstrated that in skin lesions of CTCL (mycosis fungoides), keratinocytes, endothelial cells and dermal fibroblasts showed higher expression of eotaxin-3 compared to normal skin. In some advanced cases of CTCL, atypical lymphocytes in skin lesions were found to express CCR3, the chemokine receptor for eotaxins. These patients also show higher serum levels of eotaxin-3 and eotaxin-1. Therefore, the interaction between eotaxins and CCR3 may play a role in the pathogenesis of mycosis fungoides[82].

In addition, the chemokine receptor CXCR3 has been found to be expressed in low-grade (patch and plaque stage) mycosis fungoides, especially in the epidermotropic lymphoma cells[83-85].

MANAGEMENT: SKIN-DIRECTED THERAPIES

There are a variety of different treatment strategies available for mycosis fungoides and Sézary syndrome (Table 2), depending on the severity of the disease and patient factors[86-89]. Since mycosis fungoides and Sézary syndrome are generally not curable, chronic management is required in order to control the disease. In early stage mycosis fungoides, (stages ⅠA-ⅡA), lymphoma cells are mainly confined to the skin, and skin-directed therapies are usually used. In advanced stage mycosis fungoides (stages ⅡB-ⅣB) and Sézary syndrome, systemic therapies may be selected, including immunotherapy, targeted therapies and chemotherapy[90]. Each of the different treatment strategies are associated with various adverse effects, the discussion of which is beyond the scope of this Editorial.

In early stage mycosis fungoides, topical corticosteroids is the most commonly used form of treatment[91]. It can also be used in combination with other therapies in advanced stages of disease. Topical nitrogen mustard (a DNA alkylating agent) or topical retinoids (bexarotene, tazarotene) may also be used in early stage mycosis fungoides[92,93].

Phototherapy with ultraviolet light may be effective for patients with early stage (stages ⅠA-ⅡA) mycosis fungoides. Forms of phototherapy include PUVA with oral 8-methoxypsoralen, and narrowband ultraviolet B (311 nm)[94-96].

Ionizing radiation therapy has deeper penetration compared to ultraviolet phototherapy[97]. Total skin electron beam therapy may be used for patients with rapidly progressive or refractory disease, and plaque or tumor lesions involving large body surface area[98,99]. Localized radiotherapy may be suitable for patients with localized tumor lesions[100].

MANAGEMENT: SYSTEMIC THERAPIES

The oral retinoid bexarotene is used for the treatment of refractory mycosis fungoides and Sézary syndrome in all stages[101,102]. Bexarotene acts by modulating cell differentiation and apoptosis, and also decreases the expression of CCR4 on malignant lymphocytes, which may inhibit their ability to migrate to the skin[103,104].

In mycosis fungoides and Sézary syndrome, there is an increased expression of Th2 cytokines (including IL-4, IL-5, and IL-10). IL-12 is a Th1-promoting cytokine, and has been shown to be efficacious in some patients[105]. Interferon-α may also be effective for different stages of mycosis fungoides, and act by inducing Th1-mediated immune responses to atypical lymphocytes[106].

In extracorporeal photopheresis, the circulating lymphocytes are separated from the patients' peripheral blood, 8-methoxypsoralen is added, and the cells are treated with ultraviolet-A light. This treatment is indicated for erythrodermic mycosis fungoides and Sézary syndrome[107,108].

Chemotherapy drugs may be used for refractory or progressive mycosis fungoides and Sézary syndrome. Methotrexate is an antifolate agent which acts by

inhibiting dihydrofolate reductase and thereby inhibits proliferation of lymphocytes[109]. Hematopoietic stem cell transplantation may be used in advanced stage mycosis fungoides and Sézary syndrome, and have the potential for curing the disease[110].

CONCLUSION

Mycosis fungoides and Sézary syndrome are characterized by a clonal expansion of malignant $CD4^+$ T lymphocytes with skin-homing properties, and have potential for lymph node, blood and visceral organ dissemination. Currently, treatment strategies for mycosis fungoides and Sézary syndrome are limited. The lack of effective targeted therapy results in part from the current poor understanding regarding the pathophysiology of these diseases. Since chemokines and chemokine receptors have been found to play important roles in the pathogenesis of mycosis fungoides and Sézary syndrome, they may be useful targets for the development of new treatments for these diseases[111]. Previously, antibodies against CCR4 which induce antibody-dependent cellular cytotoxicity have been used in the treatment of mycosis fungoides and Sézary syndrome[112]. In addition, chemokine-toxin fusion proteins (for example CCL17 ligated to the Pseudomonas exotoxin 38) have been demonstrated to selectively target and kill lymphoma cells which express CCR4[113]. Therefore, further investigations are warranted to determine whether modulation of chemokines and chemokine receptors may be potentially useful for the treatment of mycosis fungoides and Sézary syndrome in the future.

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