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Prevalence of cutaneous T and B cell lymphoma

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Abstract
Differentiating primary cutaneous lymphoma from secondary cutaneous lymphoma is crucial since the former develops first in the skin without any systemic involvement. Because of the clinical and histological similarities between primary and secondary cutaneous lymphomas, distinguishing between the two can be difficult. In order to prevent any diagnostic issues, it may be necessary to do thorough staging investigations.
PCTCL is more prevalent than PCBCL since seventy-one percent of cases are PCTCL (7.7 cases/million inhabitants/year), while 29 percent of cases are PCBCL (3.1 cases/million inhabitants/year), according to an American epidemiological study published in 2009; More males than females are affected by PCL, with a male-to-female ratio of 1.72 (14.0 vs. 8.2 cases/million inhabitants/year). Also, the rate is highest among blacks, lowest among Hispanic Caucasians, and intermediate among Asians, with an annual rate of 11.5, 7.9, and 7.1 cases per million people.
Blacks had a higher incidence of PCTCL (10.0 cases/million inhabitants/year) while non-Hispanic Caucasians had a higher incidence of PCBCL (3.5 cases/million inhabitants/year).
Incidence of PCL was higher in 2001-2003 (14.3 vs. 5.0 cases/million inhabitants/year) and stabilized in 2004-2005 (12.7 vs. 5.0 cases/million inhabitants/year) according to this study.

Keywords: Cutaneous lymphomas, PCTCL, CTCL

Introduction
About 65-75% of all cases of cutaneous lymphoma (CL) can be attributed to cutaneous T-cell lymphomas (CTCL). Nearly half of all cases of primary cutaneous lymphoma are diagnosed as mycosis fungoides (MF), making it the most frequent CTCL entity overall [1].
About 25% to 35% of all CL are primary cutaneous B-cell lymphomas (PCBCL). Primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle center lymphoma, and primary cutaneous diffuse large B-cell lymphoma are the three most prevalent types of CBCL.WHO classification from 2017 now includes EBV-positive mucocutaneous ulcer (EBV-MCU) as a new provisional entity among uncommon B-cell proliferations [2].
Differentiating primary from secondary cases is crucial since the former develops first in the skin without any systemic involvement. Because of the clinical and histological similarities between them, distinguishing between the two can be difficult. Therefore, comprehensive staging examinations may be necessary to prevent diagnostic issues [3].
(PCBCLs) are B lymphoma are characterized by the absence of extracutaneous illness at the time of diagnosis. About 25% to 29% of all primary cutaneous lymphomas in the US are PCBCLs; these tumors are more prevalent in males than in women, and their prevalence rises with age. Unlike mycosis fungoides, which disproportionately affects black people, PCBCL primarily affects non-Hispanic whites [4].
The clinical characteristics, prognosis, and therapy of PCBCL are vastly different from those of systemic B-cell lymphomas with secondary skin involvement. Until recently, PCBCL was incorrectly classified alongside other systemic B-cell lymphomas despite its distinct clinical characteristics. Older categorization schemes for PCBCL mirrored the state of knowledge at the time, but bigger European series led to a better grasp of the clinical distinctions [5].

Pathogenesis
The Pathogenesis of PCBCL is only partially understood. It is believed that they begin as reactive inflammatory lymph proliferative processes and that lymphoma genesis occurs in successive steps.

Hence there are ―borderline cases‖ in which it is difficult to distinguish between pseudo lymphomas (reactive lymphoid hyperplasia) and real lymphomas [6].

It appears that expression of oncogenes and/or inhibition of tumor suppressor genes, as well as an imbalance between cell proliferation and apoptosis, deregulation of major biochemical pathways for intracellular signal transmission, cell adhesion, and migration, and other factors, determine the transition from a pre-neoplastic to a neoplastic condition. Predisposing variables include chronic antigenic stimulation and viral and bacterial infections, but the underlying cause is often unknown [6].

Some lymphomas, especially those developing in immunocompromised individuals like those infected with the human immunodeficiency virus (HIV) and those who have undergone a stem cell transplant, have been linked to herpes viruses like Epstein Barr virus (EBV) and Human Herpes Virus type 8 (HHV8). One further factor that deserves attention is the possible link between PCBCL and Hepatitis C Virus (HCV) infection. PCMZL have been linked to Borrelia burgdorferi infection, but this is still a debatable topic [7].

Epidemiology

Seventy-one percent were PCTCL (7.7 cases/million inhabitants/year), and 29 percent were PCBCL (3.1 cases/million inhabitants/year), according to an American epidemiological study published in 2009. Furthermore, research demonstrated that the male to female PCL incidence ratio was 1.72 (14.0 cases/million inhabitants/year vs. 8.2 cases/million inhabitants/year). Also, the rate is highest among blacks, lowest among Hispanic Caucasians, and lowest among Asians, at 11.5, 7.9, and 7.1 cases per million people per year [6].

PCTCL had the highest prevalence among blacks (10.0 cases/million inhabitants/year), while PCBCL had the highest incidence among non-Hispanic Caucasians (3.5 cases/million inhabitants/year) [6].

This consensus classification system distinguishes the following 3 main types of PCBCL [2]

PCMZL and PCFCL are recognized as indolent lymphomas, while PCDLBCL-LT has a more intermediate behavior.

Primary cutaneous follicular center lymphoma

PCFCL is the most frequent B-cell lymphoma to arise as a primary tumor of skin, accounting for roughly 55% of all PCBCLs, and follicular lymphoma is the second most common lymphoma found in developed countries [2].

Clinical features

Individual or clusters of papules, plaques, or nodules are the hallmarks of PCFCL. Scalp, forehead, neck, and trunk lesions are more common than lesions on the legs. In some cases, we have patients with multifocal lesions. Lesions can be anything from small pink papules to larger, purple nodules. The average age of patients diagnosed is 60 years old [8].

In major trials, the 5-year survival rate for PCFCL has reached 95%, which is very encouraging. In some circumstances, PCFCL lesions may shrink or remain stable even in the absence of treatment. Between 5 and 10 percent of cases involve spread to non-cutaneous areas. The prognosis of patients with multifocal lesions is not worse than that of those with single lesions (Figure 1) [4]. Similarly, there is no difference in prognosis based on the histologic development pattern. The prognosis for patients with PCFCL of the leg is poor, with a 5-year disease-specific survival rate of 41% [9].

In some cases, PCFCL will develop into DLBCL, and in others, the two diseases will coexist. Although rarely aggressive, relapse following treatment occurs in up to 46.5% of patients. It's important to remember that recurrence has no bearing on prognosis and is typically localized to the skin [9].

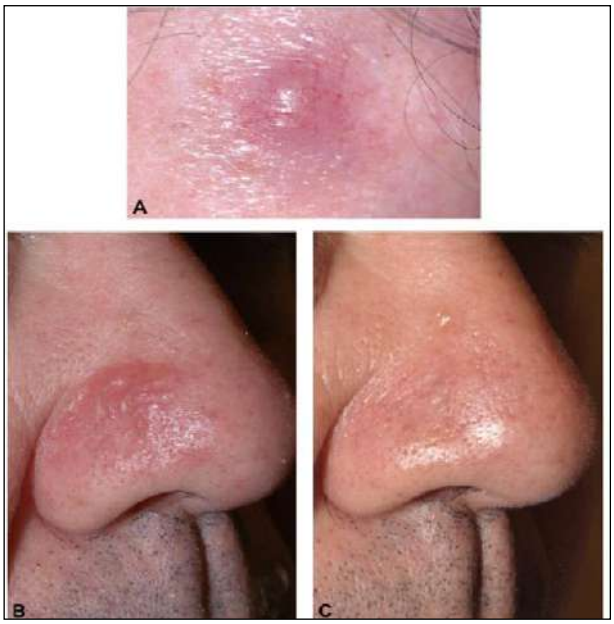


Fig 1: Primary cutaneous follicle center lymphoma. A. Pink tumor nodule on the anterior aspect of the scalp. B. Rhinophyma-like lesion on the nose. C. Spontaneous resolution of the lesion after 6 months [4].

Primary cutaneous marginal zone lymphoma

Zone of primary marginalization of the skin Lymphoma is classified as either a mucosa-associated lymphoid tissue (MALT) lymphoma or a skin-associated lymphoid tissue (SALT) lymphoma, both of which are considered extra nodal marginal zone B-cell lymphomas. PCMZLs are tumors that were formerly classified as immunocytomas or plasmacytomas. These entities are now recognized as PCMZL variations with many plasma cells [10].

Clinical features

Typically found on the trunk (46%), arms (13%), and head (7%), primary cutaneous marginal zone lymphoma manifests as red to violaceous isolated papules, plaques, or nodules. Most lesions occur on their own (48%). The median age upon diagnosis is 55 (67), and men are twice as likely as women to be affected. Children can develop marginal zone lymphomas, and their disease course is comparable to that of adults. Patients over the age of 65 who report with head and neck lesions should undergo a more thorough work up and monitoring to rule out extra cutaneous disease because of the higher prevalence of nodal MZL in this patient population [11].

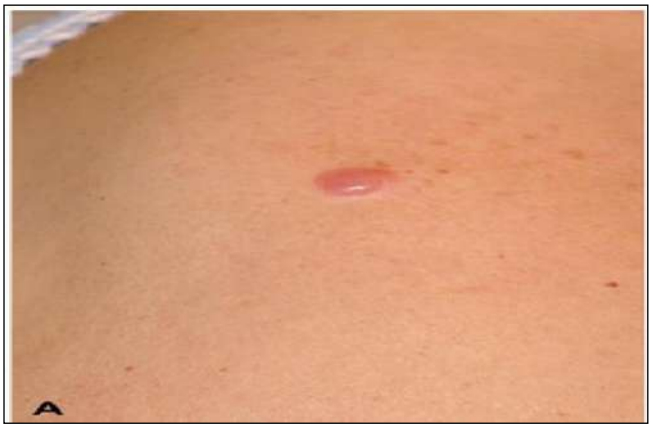


Fig 2: Primary cutaneous marginal zone lymphoma (Red papule on the arm) [4].

Primary cutaneous diffuse large B-cell lymphoma, leg type

An aggressive form of PCBCL, primary cutaneous diffuse large B-cell lymphoma, leg type manifests itself on the legs and is characterized by a proliferation of cells that are disproportionately big and have round nuclei. PCDLBCL-LT, in contrast to PCFCL, has few T cells. PCFCL that progressed to PCDLBCL has been reported on extremely infrequently [12].

Clinical features

Leg-type primary cutaneous diffuse large B-cell lymphoma manifests as nodules, plaques, or tumors ranging in color from red to blue on one or both legs. Women are at a higher risk than men are (2:1), and the average patient is 76 years old when symptoms first appear. Skin nodules, tumors, and deeply infiltrating plaques are all possible clinical manifestations. Verrucous plaque-like lesions, numerous nodules with broad garland-like lesions, and a bluish-reddish multicolored rainbow pattern are only a few of the unique manifestations described in case reports. Ten percent to fifteen percent of patients report lesions elsewhere other than the legs [13]. The prognosis for primary cutaneous diffuse large B-cell lymphoma, leg type is worse since it often spreads to non-cutaneous areas and the 5-year survival rate is just around 50% [14].

Treatment [15, 16]

Primary cutaneous B-cell lymphoma (PCBCL) is treated with a wide variety of strategies, from targeted therapies in indolent cases (PCFCL and PCMZL) to multi agent chemotherapy and immune-based modalities in aggressive cases (PC-DLBCL leg or other/non leg type). Whether or not the indolent PCBCL is a single, localized lesion also determines how it should be treated. Although PCFCL and PCMZL both frequently experience relapses, overall survival rates remain very high. The prognosis for primary cutaneous DLBCL is substantially worse, even with intensive treatment.

Primary cutaneous follicle center lymphoma [17]

Radiation therapy and surgery, with the goal of cure, are the primary lines of treatment if the cancer is localized. It is not uncommon for skin cancer to return following treatment, frequently in an unaffected area. Multiple lesion patients can be observed, treated locally, radiated, treated topically, treated intralesionally, or treated systemically. Table (1).

Table 1: Recommendations for the treatment of primary cutaneous follicle center lymphoma [18]

CBCL type and extent	Initial therapy	Secondary therapy
Solitary/localized	Local radiotherapy and excision Select cases-observation, topical therapy (eg, steroids, imiquimod, nitrogen mustard, and bexarotene), and intralesional steroids	Observation, intralesional interferon-alfa, excision, intralesional rituximab, topical therapy (eg, steroids, imiquimod, nitrogen mustard, and bexarotene), intralesional steroids and local radiotherapy,
Generalized skin disease	Observation, intravenous rituximab, local radiotherapy, topical therapy (eg,steroids, imiquimod, nitrogen mustard, and bexarotene), and intralesional steroids	Chlorambucil with or without rituximab or CVP with or without rituximab Select cases-CVP

Abbreviations: CBCL, Cutaneous B-cell lymphoma; CVP, cyclophosphamide, vincristine, and prednisone.

Primary cutaneous marginal zone lymphoma [19]

Radiation therapy (RT), curative surgery, and sometimes antibiotics are all viable options for patients with localized or locally-confined disease. Those with PCMZL may experience higher relapse rates after targeted treatment than those with PCFCL. Multifocal illness treatment options include monitoring, radiation therapy, topical medications, intralesional steroids, and systemic immunomodulators or chemotherapeutics. Table (2).

Table 2: Recommendations for the treatment of primary cutaneous marginal zone lymphoma [19]

CBCL type and extent	Initial therapy	Secondary therapy
Solitary/localized	Local radiotherapy, excision, and antibiotics Select cases-observation, topical therapy (eg, steroids, imiquimod, nitrogen mustard, and bexarotene), and intralesional steroids	Observation, intralesional interferon-alfa, excision, intralesional rituximab, topical therapy (eg, steroids, imiquimod, nitrogen mustard, and bexarotene), intralesional steroids, andlocal radiotherapy
Multifocal skin disease	Observation, intravenous rituximab, local radiotherapy,chlorambucil antibiotics, topical therapy (eg, steroids, imiquimod, nitrogen mustard, and bexarotene), and intralesional steroids	Intralesional interferon-alfa, intravenous rituximab, topical steroids, intralesional steroids, chlorambucil with or without rituximab, and CVP with or without rituximab Select cases-CVP

Abbreviation CBCL: Cutaneous B-cell lymphoma. CVP: cyclophosphamide, vincristine, and prednisone

Primary cutaneous diffuse large B-cell lymphoma, leg-type [20]

Relapses in the skin are common, and PCDLBCL-LT often spreads quickly. First-line therapy for isolated, regional, or systemic illness is radiotherapy (RT) alone or in conjunction with R-CHOP. DLBCL clinical trials using experimental treatments show promise. Table (3)

Table 3: Recommendations for the treatment of aggressive primary cutaneous B-cell lymphoma [21].

CBCL type and extent	Initial therapy	Secondary therapy
Solitary/localized	R-CHOP with local RT or local RT or clinical trial	R-CHOP (if not previously received) or RT to previously un irradiated tumor
Generalized	R-CHOP with or without local RT or clinical	Trial Local RT for palliation or radio immunotherapy

Abbreviation CBCL: Cutaneous B-cell lymphoma; R-CHOP: rituximab; cyclophosphamide, hydrochloride, prednisone, doxorubicin, and onvocin/vincristine, with RT, radiotherapy.

Cutaneous T cell lymphoma

Approximately 75% of primary cutaneous lymphomas are T-cell derived, two-thirds of which may be classified as Mycosis fungoides (MF) or Sézary Syndrome (SS) [23].

Mycosis fungoides (MF), the most common cutaneous T cell lymphoma (CTCL) and often referred to by the latter term, is characterized by clonal proliferation of skin homing mature T cells, mostly CD4 positive, with special predilection for involving the epidermis. Although the vast majority of the patients diagnosed are 50 years or older, children can also be affected by this lymphoma [23].

Epidemiology

Most occurrences of cutaneous lymphoma are caused by MF, which accounts for 3.9% of all non-Hodgkin lymphomas. The annual age-adjusted incidence of CTCL in the United States is between 6.4% and 9.6%, and it has been on the rise since 1973. The median age at diagnosis for MF is between 55 and 60 years old, and the male to female ratio is 2:1 [24].

The frequency in the United States was estimated to be between 0.77 and 0.87 per 100,000 people per year based on data from a few states, whereas other states reported an incidence of only 0.64 per 100,000 people per year. The projected incidence in Europe was between 0.29 and 0.39 per 100,000 people per year, and it may rise in the future[25]. Seventy percent of patients are white, with 14% being black, 9% being Hispanic, and 7% being Asian in the United States. A second lymphoma, especially Hodgkin lymphoma and the CTCL subtype lymphomatoid papulosis, and other non-hematologic cancers are much more likely to occur in patients with MF and SS [26].

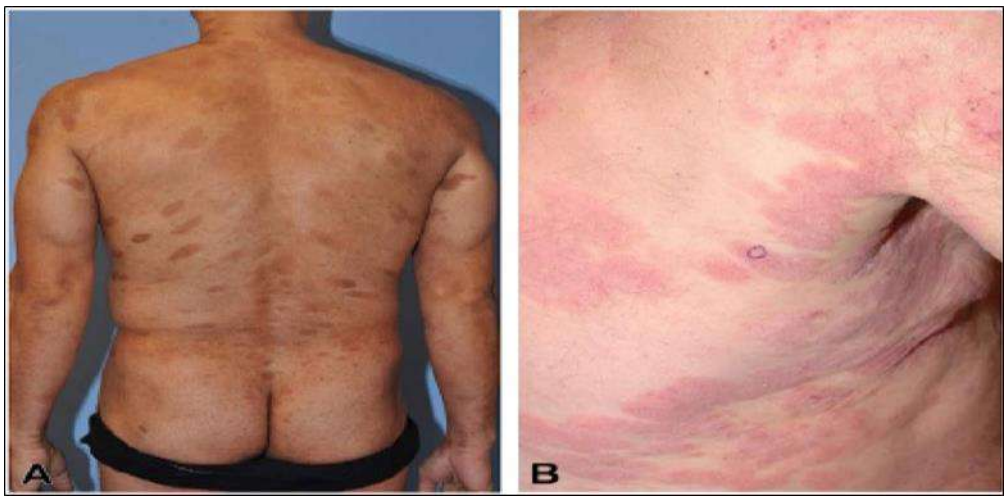
Etiology

The buildup of T cell helper memory cells in the skin, following prolonged antigenic stimulation, is thought to be at the root of MF. Dendritic cell counts were higher in preclinical MF lesions, lending credence to this theory. Antigen-presenting cell, to be precise. Toll-like receptor (TLR) 2, 4, and 9 expression by keratinocytes is elevated in individuals with MF, as is the expression of certain human leukocyte antigen (HLA) class II alleles, according to other studies [27]. Psoriasis and chronic allergic contact dermatitis are two examples of inflammatory skin diseases in which Toll-like receptor stimulation has been observed [28]. There have been reports of lymphomatoid reactions due to contact hypersensitivity, but no link between contact dermatitis or other inflammatory skin disorders and MF/SS has been established [26].

Possible infectious causes of MF include Staphylococcus aureus and related enterotoxins. Patients with erythrodermic MF (EMF) and SS had a significant colonization rate with S. aureus, and this study also indicated that erythroderma and the severity of skin disease improved clinically following antibiotic treatment [29]. While the impact of occupational characteristics such working in the glass, pottery, and ceramics industries in MF has been investigated, it is still debatable. Herbicide exposure, which is common in the military, has been associated to non-Hodgkin lymphoma, but not CTCL in particular [30].

Classic mycosis fungoides

Mycosis fungoides (MF) is the most common and least aggressive form of CTCL, with an annual incidence rate of about 0.5 for every 100,000 people in developed countries. Well-defined, pruritic erythematous patches are the hallmark of classic MF, which typically develops slowly over the course of years or even decades and typically affects areas that are not exposed to the sun, such as the breasts, buttocks, lower trunk, and groin (Fig. 3). These spots can progress into infiltrative plaques and tumors, and it's not uncommon to find all three lesion forms together [26].



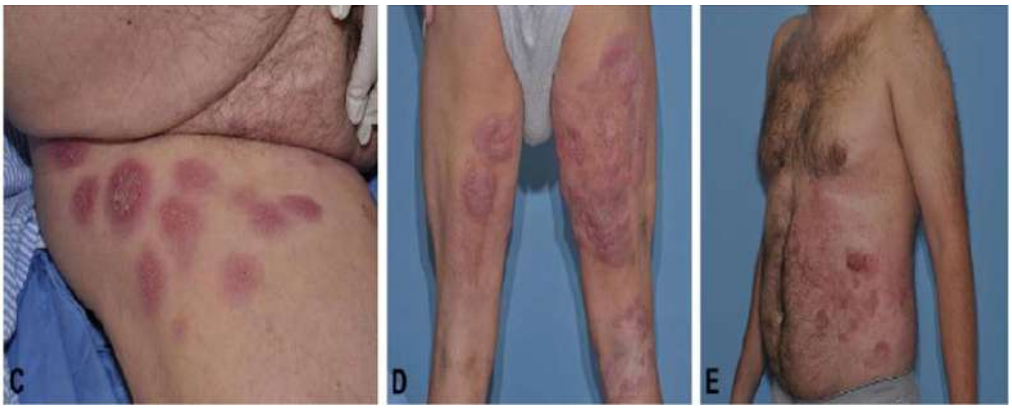


Fig 3: Mycosis fungoides patients presenting with disseminated patches (A), plaques (B and C), and tumors (D and E). All 3 lesion types can be seen concomitantly (E) [26].

Lymphocytes with cerebriform nuclei and a haloed appearance that exhibit epidermotropism or occupy the dermoepidermal junction are diagnostic of classic mycosis fungoides. Reactive T lymphocytes and other immune cells are common in the early stages of mycosis fungoides (21), which may cause confusion with chronic inflammatory dermatoses. Atypical T cells lack CD4, CD45, and sometimes CD2, CD5, and/or CD7, yet express CD4 and CD45 [31].

Treatment

Mycosis fungoides (MF) and Sézary syndrome (SS) treatment decisions are based on a number of factors, including the severity of the condition, its effect on the patient's quality of life, their prognosis, and their age and other medical conditions. The prognosis for MF is good when diagnosed at an early stage (IA-IIA) and treated with skin-directed medicines as the first line of defense. Although a cure for the disease is unknown, long-term full remissions have been achieved [32].

Treatment for advanced stage MF/SS (stages IIB-IVB) aims to reduce the tumor burden, halt disease progression, and preserve quality of life, however the prognosis is poor. Immunobiologic and targeted medicines are currently in use; nevertheless, the clinical response time is generally brief. Only patients who have not responded to other treatments should undergo single- or multiple-agent chemotherapy. Treatment options for MF/SS that are consistent with the NCCN guidelines have been included in the revised guidelines by the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC), and the Cutaneous Lymphoma Task Force of the European Organization for Research and Treatment of Cancer (EORTC) [32].

Skin directed therapies [32]

Topical corticosteroids (T1a and T2a)

Despite its popularity, only one randomized controlled trial has compared the efficacy of this high-potency medication to that of less-potent topical steroids. Primarily, clobetasol propionate is what is used. For individuals with few patches or plaques, this treatment is straightforward.

Photodynamic therapy and Imiquimod 5% cream (based on individual case reports).

Phototherapy

When it comes to treating early MF, UVB is one of the most effective options, especially for the stage-specific patchiness of T1a and T2a. Plaque disease (T1b, T2a) and patients with dark skin are still encouraged to use PUVA.

Localized radiotherapy (RT)

Provide good relief for isolated lesions and, in some cases, complete resolution of a single lesion.

Table 4: Skin-directed therapies for the treatment of mycosis fungoides/ Sézary syndrome [32]

Skin-Directed Therapies	Overall Response Rate (%)
Topical superpotent corticosteroids	75–95
Bexarotene gel	50–75
Nitrogen mustard/mechlorethamine HCl gel	50–90
Imiquimod cream	50
Tazarotene cream	58
Narrow-band UVB	54–90
PUVA	85–100
Radiation therapy (local external electron beam, brachytherapy, total skin electron beam therapy)	—

Abbreviations: HCl, hydrochloride; PUVA, psoralen UVA.

Systemic therapies [32, 33]

Interferon-α (IFN-α)

Is the most prescribed medication, albeit different dosing schedules apply to it? As a starting point, the EORTC suggests 3 million units three times weekly. The response rate can be anywhere from zero to eighty percent. Patients with eosinophilia can benefit greatly from its treatment because of its ability to suppress eosinophil chemotaxis and activation.

Bexarotene

Prescription of bexarotene is restricted to those who have already been treated with interferon. The use of isotretinoin and acitretin is also widespread. Drying of the skin and mucosa, hyperlipidemia, and central hypothyroidism are the

key adverse effects behind the teratogenic impact. The combination of these drugs with PUVA results in a higher rate of complete remission.

Total skin electron beam therapy (TSEB)
Attenuated electrons produced by a linear accelerator penetrate the epidermis to a shallow depth, sparing interior organs. Low-dose therapy has been argued for and against standard-dose treatment.

Low-dose Methotrexate (MTX)
In refractory MF, this cytotoxic therapy is often utilized either alone or in combination with IFN. The typical weekly dosage is 10-25 mg.

Combinations of these treatments
Treatments that combine PUVA and retinoids, or less traditionally combine IFN and retinoids (acitretin), are the most common. Methotrexate (Mtx) has also been used in conjunction with interferon beta, light therapy, and radiation therapy. These systemic treatments are frequently used with topical ones.

Table 5: Systemic therapies used to treat mycosis fungoides/ Sézary Syndrome [32]

Systemic Therapies	Overall Response Rate
Bexarotene	ORR 45%, CR 13%
IFN a	ORR 64%; CR 27% in stage IA–IVA
Romidepsin	ORR 38%, CR 6%
Methotrexate	ORR 58%, CR 41% in erythrodermic MF ORR 33%, CR 12% in plaque-stage MF
Brentuximab vedotin	ORR 65%, CR 10%
Pralatrexate	ORR 41%, CR <1%
Doxorubicin	ORR 30% to 80%, CR 20% to 60%
Gemcitabine	ORR 51.0%–70.5%, CR 11.5%–23.0%
Pembrolizumab	ORR 38%, 1 CR
Bortezomib	ORR 67%, CR 17%

Abbreviations: IFN, interferon; ORR, overall response rate.

According to the NCCN, there is a dearth of medicines offering long-lasting responses for the treatment of MF/SS. There is a wide range of response rates from 30% to 67% with no more than 41% of patients seeing a complete response after receiving a targeted therapy (56). Even if the response rate is higher with conventional chemotherapy, any benefits would likely be temporary and would lead to poorer long-term results. The only treatment that has shown promise for curing CTCL is non myeloablative allogeneic stem cell transplantation, with a 5-year overall survival rate of 46% [22].

Conclusion
A wide variety of lymphoid malignancies, lymphomas exhibit a variety of clinical behaviours and therapeutic effects. The prognosis is influenced by the histologic type, clinical factors, and more recently, molecular characteristics. According to the WHO classification, lymphoid neoplasms can be classified as either being of B-cell or T-cell origin, depending on whether they were produced from mature lymphoid cells or precursor lymphoid cells. Treatment differs according to the type and subtype of lymphoma.

Conflict of Interest
Not available

Financial Support
Not available

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