Primary Skin Lymphomas

Drs. Eugenia Piliotis, Kevin Imrie, Neil Shear, Scott Walsh & Matthew Cheung
Updated May 2007*

Updates:
- New staging criteria
- Updated treatment recommendations

Introduction

The skin is the second most common extranodal site of lymphoma after the gastrointestinal tract with an estimated incidence of 0.5-1/100,000 [1]. The lymphomas of the skin are a heterogeneous group of malignancies of T and B cell origin. Primary skin lymphomas must be differentiated from lymphomas with secondary skin involvement as they differ in presentation, histology and prognosis [2, 3]. Because of these differences a classification system for skin lymphomas has recently been published by the World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC) [4-6].

Classification

The skin lymphomas fall into the following categories according to the WHO-EORTC classification [4-6].

Table 1.

WHO-EORTC classification of cutaneous lymphomas with primary cutaneous manifestations

Cutaneous T-cell and NK-cell Lymphomas
Mycosis fungoides
MF variants and subtypes
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome preceded by MF /secondary Sézary syndrome
Sézary syndrome
Primary cutaneous $CD30^+$ lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma*
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma (provisional)
Cutaneous γ/δ T-cell lymphoma (provisional)
Primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma (provisional)
Primary cutaneous peripheral T-cell lymphoma, unspecified, other
Cutaneous B-cell lymphoma
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other
Intravascular large B-cell lymphoma
Precursor hematologic neoplasm
$CD4^+/CD56^+$ hematodermic neoplasm (blastic NK-cell lymphoma)†

*Original treatment policy prepared by Drs. K. Imrie, N. Shear, R. MacKenzie & G. Jones, updated 2005 by Drs. K. Imrie, N. Shear, R. MacKenzie & J. Sussman

Table 2.

Relative frequency and disease-specific 5-year survival of 1905 primary cutaneous lymphomas classified according to the WHO-EORTC classification [6]

WHO-EORTC Classification	No.	Frequency, %*	Disease-specific 5-year survival, %
Cutaneous T-cell lymphoma			
Indolent clinical behavior			
Mycosis fungoides	800	44	88
Folliculotropic MF	86	4	80
Pagetoid reticulosis	14	< 1	100
Granulomatous slack skin	4	< 1	100
Primary cutaneous anaplastic large cell lymphoma	146	8	95
Lymphomatoid papulosis	236	12	100
Subcutaneous panniculitis-like T-cell lymphoma	18	1	82
Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma†	39	2	75
Aggressive clinical behavior			
Sézary syndrome	52	3	24
Primary cutaneous NK/T-cell lymphoma, nasal-type	7	< 1	NR
Primary cutaneous aggressive $CD8^+$ T-cell lymphoma†	14	< 1	18
Primary cutaneous γ/δ T-cell lymphoma†	13	< 1	NR
Primary cutaneous peripheral T-cell lymphoma, unspecified‡	47	2	16
Cutaneous B-cell lymphoma			
Indolent clinical behavior			
Primary cutaneous marginal zone B-cell lymphoma	127	7	99
Primary cutaneous follicle center lymphoma	207	11	95
Intermediate clinical behavior			
Primary cutaneous diffuse large B-cell lymphoma, leg type	85	4	55
Primary cutaneous diffuse large B-cell lymphoma, other	4	< 1	50
Primary cutaneous intravascular large B-cell lymphoma	6	< 1	65

NR indicates not reached.
*Data are based on 1905 patients with primary cutaneous lymphoma registered at the Dutch and Austrian Cutaneous Lymphoma Group between 1986 and 2002.
†Primary cutaneous peripheral T-cell lymphoma, unspecified excluding the three provisional entities indicated with a double dagger (‡).

Mycosis Fungoides/Sézary Syndrome

Mycoses fungoides and Sézary syndrome together make up approximately half of all cases of cutaneous lymphomas. There is a wide range of clinical presentations as well as tempo of disease progression. The diagnosis is also often difficult to make pathologically, thus it is not unusual for patients with MF to remain undiagnosed for several years or even decades.

Mycosis Fungoides

Diagnosis

The diagnosis of mycosis fungoides (MF) can be difficult and may require repeated biopsies of multiple affected areas. The diagnosis is made by clinical pathologic correlation. Usually lesions are well-defined patches or plaques, often in non-sun exposed areas, and have features of poikiloderma (dyspigmentation, atrophy). There are 50 described clinical presentations, such as acquired ichthyosis and bullous lesions; therefore a dermatologist should be consulted. Preferably several biopsies of skin lesions are done to help establish the clinical diagnosis. If there is more than one type of lesion morphology, it is appropriate to biopsy each type at least once (e.g., patch, plaque or tumour). Biopsy material from the skin should be evaluated by a dermatopathologist or hematopathologist with expertise in skin lymphomas. Immunohistochemistry should be performed.

The typical features of MF include epidermotropic, band-like infiltrates involving the papillary dermis, containing atypical small, medium sized and occasionally large mononuclear cells with hyperchromic, indented, cerebriform nuclei and variable numbers of admixed inflammatory cells. Colonization of the lower layers of the epidermis by single or small groups of neoplastic cells is a characteristic finding. Atypical cells can cluster in the epidermis surrounding Langerhans cells creating Pautrier microabscesses. With progression to tumour stage, the dermal infiltrates become more diffuse and the proportion of tumour cells may increase in numbers and size. Tumour cells are typically T helper cells expressing $CD3^+$, $CD4^+$, $CD45RO^+$, $CD8^-$, and $CD30^-$. Loss of mature T cell antigens such as CD7 and CD26 is also a common feature. TCR genes are clonally rearranged in most cases [4, 6].

Baseline Investigations

The following baseline investigations should be performed:

- Thorough history and physical examination
- Mapping of skin lesions (see below)
- CBC, differential & blood film
- Liver function tests, calcium profile, renal profile, LDH
- CT scan of chest, abdomen, and pelvis (in patients with >= stage II disease)
- Serology for HTLV-1 is recommended, and must be performed if ATLL is suspected
- Biopsy of enlarged lymph nodes
- Peripheral blood flow cytometry for CD4/CD8 ratio
- Bone marrow biopsies should be restricted to patients with unexplained blood count abnormalities, significant blood involvement (B2), or suspected diagnoses other than MF (ATLL, PTCL-NOS, etc.).

Staging [4]

Table 3. ISCL/EORTC Revision to the Classification of Mycosis Fungoides & Sézary Syndrome

TNMB Stages	
Skin	
T_1	Limited patches,* papules, and/or plaques† covering < 10% of the skin surface. May further stratify into T_{1a} (patch only) vs T_{1b} (plaque ± patch).
T_2	Patches, papules or plaques covering >=10% of the skin surface. May further stratify into T_{2a} (patch only) vs T_{2b} (plaque ± patch).
T_3	One or more tumours‡ (> = 1 cm diameter)
T_4	Confluence of erythema covering > = 80% body surface area

TNMB Stages	
Node	
N_0	No clinically abnormal peripheral lymph nodes§; biopsy not required
N_1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0-2
N_{1a}	Clone negative#
N_{1b}	Clone positive#
N_2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3
N_{2a}	Clone negative#
N_{2b}	Clone positive#
N_3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN4; clone positive or negative
N_x	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation¶ and organ involved should be specified)
Blood	
B0	Absence of significant blood involvement: < = 5% of peripheral blood lymphocytes are atypical (Sézary) cells‖
B_{0a}	Clone negative#
B_{0b}	Clone positive#
B1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B_{1a}	Clone negative#
B_{1b}	Clone positive#
B2	High blood tumor burden: >=1000/µL Sézary cells‖ with positive clone# (Or CD4/CD8 ratio > 10)

* For skin, patch indicates any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.

† For skin, plaque indicates any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikiloderma should be noted. Histologic features such as folliculotropism or large-cell transformation (> 25% large cells), $CD30^+$ or $CD30^-$, and clinical features such as ulceration are important to document.

‡ For skin, tumor indicates at least one 1-cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histologic evidence of large-cell transformation has occurred. Phenotyping for CD30 is encouraged.

§ For node, abnormal peripheral lymph node(s) indicates any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed or 1.5 cm or larger in diameter. Node groups examined on physical examination include cervical, supraclavicular, epitrochlear, axillary, and inguinal. Central nodes, which are not generally amenable to pathologic assessment, are not currently considered in the nodal classification unless used to establish N_3 histopathologically.

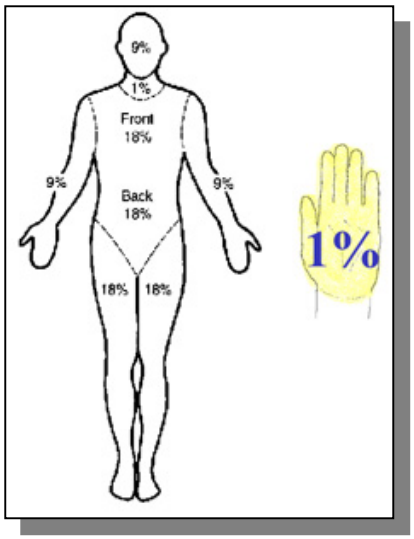
¶ For viscera, spleen and liver may be diagnosed by imaging criteria.

‖ For blood, Sézary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. If Sézary cells are not able to be used to determine tumor burden for B_2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead: (1) expanded $CD4^+$ or $CD3^+$ cells with CD4/CD8 ratio of 10 or more, (2) expanded $CD4^+$ cells with abnormal immunophenotype including loss of CD7 or CD26.

A T-cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene.

Skin Involvement

The extent of skin involvement will be determined using the rule of 9's below.



Nodal Involvement

Nodal involvement by mycoses fungoides is often challenging to determine as many patients with extensive skin involvement can have reactive lymphadenopathy or what is otherwise known as dermatopathic lymphadenopathy. Below is the criteria used by the ISCL/EORTC to determine histologic grade. Both the Dutch system and the NCI classification differentiate stages of nodal involvement based on the degree of atypical lymphocytic infiltrates seen, and the degree of effacement of normal nodal architecture. Patients with N3 nodal involvement clearly have a poorer prognosis, but it is unclear if earlier stage lesions impact overall prognosis. Furthermore, it is also unclear how the more sensitive PCR techniques to detect clonal TCR gene rearrangements independently affect prognosis [4].

Table 4. Histopathological Staging of Lymph Nodes in Mycosis Fungoides & Sézary Syndrome

Updated ISCL/EORTC Classification	Dutch System	NCI-VA Classification
N_1	Grade 1: dermatopathic lymphadenopathy (DL)	LN_0: no atypical lymphocytes LN_1: occasional and isolated atypical lymphocytes (not arranged in clusters) LN_2: many atypical lymphocytes or in 3-6 cell clusters
N_2	Grade 2: DL; early involvement by MF (presence of cerebriform nuclei > 7.5 µm)	LN_3: aggregates of atypical lymphocytes; nodal architecture preserved
N_3	Grade 3: partial effacement of LN architecture; many atypical cerebriform mononuclear cells (CMCs) Grade 4: complete effacement	LN_4: partial/complete effacement of nodal architecture by atypical lymphocytes or frankly neoplastic cells

Blood Involvement

The cut-off of 5% for blood involvement remains controversial, but is generally accepted. Another indication of significant blood involvement is a CD4:CD8 ratio grater than 10.

TNM Staging System

Table 6. ISCL/EORTC Revision to the Staging of Mycosis Fungoides & Sézary Syndrome

	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
II	1,2	1,2	0	0,1
IIB	3	0-2	0	0,1
III	4	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA1	1-4	0-2	0	2
IVA2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

Table 7. A simplified staging system has been proposed by Sausville et al [7]

Category	Definition	Median Survival
Low-risk	Limited skin disease only (IA-IIA)	10-12 yrs
Intermediate	Stage III	5 yrs
High-risk	Nodal or visceral involvement (IV)	2 yrs

The TNM Staging system, or the simplified system of low, intermediate and high-risk patients, contains groupings that are heterogenous in survival and so should be used with caution when trying to estimate prognosis. For example, patients with Stage IA disease can expect a median overall survival chance in excess of 20 years, for IB around 16-20 years from diagnosis. Even so, at least 1% of IA will die from MF by 15-years; 7% of IB. Survival with Stage IVB is very poor, typically less than a year, though 10% of such patients are alive 10-years or more following biopsy confirmed IVB disease.

Treatment

Therapy of mycosis fungoides offers symptomatic improvement of skin lesions, but has not been proven to affect the natural history of the disease [8-10]. While multiple treatment modalities exist, there is little comparative data to establish best practice. We will summarize data for each modality and identify recommended approaches for each stage. These recommendations are made based on consensus of members of our network in Toronto and Hamilton after review of the published literature that is generally of poor quality.

Treatment Modalities

1. Observation

Not all MF lesions require treatment. Patients with low risk disease whose lesions are asymptomatic do not necessarily require treatment. There is no evidence therapy changes natural history in such patients [11, 12].

2. Topical Immunomodulators

Topical corticosteroids: Are an effective option in minimally symptomatic limited patch-stage disease [13]. Response rates of over 90% with complete remission rates of over 60% have been reported for patients with stage 1A disease. High potency preparations such as clobetasol propionate 0.05% are recommended, since the effect desired is death of the causal T-cells, and not just anti-inflammation. Milder steroids or topical calcineurin inhibitors may decrease autoimmunity locally, and not treat the disease. But high potency agents lead to local side effects (such as skin atrophy), especially in sensitive

areas, such as the face, axillae or groin. Milder potency corticosteroids are more appropriate for these areas.

Topical Retinoids: Are also available and have been shown to be efficacious in early stage disease. Topical Bexarotene (Targretin®) has been shown to achieve response rates of 50% in early stage disease [14]. Topical retinoids can also be used to potentiate light therapy, especially in areas of thicker plaques. Bexarotene is not available in Canada, however topical Tazarotene (Tazorac®) and topical Tretinoin (Stieva A®) are available and are viable alternatives.

Topical Imiquimod (Aldera®): Originally formulated for the treatment of genital warts, it has shown increasingly to have efficacy in several skin malignancies. As it induces localized alpha Interferon it also has efficacy in cutaneous lymphoma [15].

Topical chemotherapy: Nitrogen mustard has been used topically since 1959 [16]. Its mechanism of action topically is uncertain and does not appear to relate wholly to its alkylating agent properties. Response rates of 80% have been reported, however it is highly allergenic and contact dermatitis is risk. Furthermore it is no longer widely available [17]. BCNU (Carmustine) had also been used as a topical alternative. Topical chemotherapies are currently more of historical interest as less cumbersome and equally efficacious treatment modalities are available.

3. Retinoids

The term retinoids refers to the entire set of vitamin A derived compounds and are physiological regulators of a large number of essential biologic processes [18]. Traditional retinoids which works through the RAR receptor such as Isotretinoin (Accutane®) have activity in MF with response rates of 40-70% in limited stage disease. Isotretinoin is typically given in doses of 20-80 mg/day PO. Patients must be counseled on the toxicities of this agent including risk of teratogenicity, hyperlipidemia, headache, personality changes, dryness of the skin and mucous membranes, fatigue, arthralgias and bone changes. Patients on retinoids need to have lipids monitored and may require treatment with an agent such as Atorvastatin (Lipitor®) 20 mg OD and female patients must be counseled to use 2 methods of birth control while taking this agent. Bexarotene (Targretin®) is a retinoid that interacts with the RXR receptor and is approved for use in CTCL by the US FDA. This agent is not routinely available in Canada. It is typically administered orally in a dose of 300 mg/m^2 daily. Reported response rates from phase II trials range from 45-54% with responses being observed in retinoid refractory and advance stage patients [19, 20]. The most common side effects with this agent are hyperlipidemia (82%), hypothyroidism (29%), and leucopenia (11%). Currently there is no definitive evidence that one retinoid is superior to another, therefore given the cost and limited availability of Bexarotene, Isotretinoin will generally be used as the first-line retinoid in our practice.

4. Phototherapy

Phototherapy has an established role in the management of CTCL. Two forms of phototherapy are in common use – Psoralen (either oral or bath) and ultraviolet A irradiation (PUVA) and narrowband ultraviolet B (NB-UVB). The greatest experience has been with PUVA, although published data is remarkably scant and is limited to small case series. Response rates of up to 70% are reported [21]. In our Centre, Psoralen will be administered by bath in most cases. The starting dose of light treatment will depend on Fitzpatrick skin type and will be increased by 0.5-1 J/cm^2, as tolerated. NB-UVB will typically be administered three times per week until lesions clear and then the frequency decreased accordingly. PUVA is initiated at 2 sessions per week and maintenance is possible with once per month treatments. It may take about 20 treatments to achieve clearing. Side effects of Psoralen include nausea and vomiting when given orally. The major risk of PUVA is the potential for development of non-melanomatous and melanomatous skin cancers after long-term exposure and patients must be made aware of this risk [22, 23]. PUVA treatments therefore are limited to approximately 200 to 250 exposures. NB-UVB may be comparable to PUVA in efficacy and does not require Psoralen, making it less cumbersome and better tolerated. The risk of skin cancer remains to be clarified, but recent data suggest the risk is much lower than with PUVA. The decision to use NB-UVB or PUVA in a given patient will be tailored to the specific patient's circumstances.

5. Interferons

The interferons have demonstrated activity in CTCL [24]. Interferon-alpha is the best studied agent with response rates of 45-70% reported with doses ranging from 2 MU tiw to 18 MU daily. A common dosing strategy is to begin with 1-2 MU/m2 tiw and titrate up to 3 MU/m² tiw. The dose can be pushed to 5 MU/m² tiw if response is suboptimal and side effects are not limiting. Interferon alpha is commonly combined with other therapies such as retinoids, PUVA, TSEB, or extracorporeal photophoresis (ECP) with evidence of synergistic effect [25]. Less experience has been published with Interferon gamma, but in small phase II trials; response rates of 30-60% have been observed.

6. Radiation therapy

Radiotherapy is the single most active agent in the treatment of MF [26]. Involved field radiation of uni-lesional MF (rare) can be curative, and can be effective in controlling individual lesions. It may be used as a single modality in the case of limited (generally stage 1A) disease or in combination with other treatment modalities. Involved field irradiation will commonly be added to other therapies in the treatment of tumor stage disease or lymph node enlargement.

Total skin electron beam radiation (TSEB) is another method of administering radiation for patients with MF. This form of therapy offers complete response rates of 40-90% with as many as 50% of patients with limited plaque disease and ~25% of patients with generalized plaque disease remaining disease free for many years and even decades. This form of therapy is time consuming and has significant toxicities with erythema, dry skin desquamation and alopecia being the most common side effects, as well as increasing the risk of secondary skin malignancies. Therefore TSEB is commonly reserved for patients with very thickened plaques and those who fail to respond to topical therapy or phototherapy.

7. Extracorporeal photopheresis (ECP)

Photopheresis is a procedure that exposes white blood cells exposed to 8-methoxypsoralen to an ultraviolet light source using a pheresis device [27]. The procedure typically takes 2-3 hours and is repeated at 4 weekly intervals. The published data consists of small single arm trials. The pooled response rate from such studies is 55.7% with significant responses observed in high-risk patients with significant blood involvement.

8. Systemic chemotherapy

Chemotherapy regimens used in MF include oral alkylators antimetabolites, purine analogs, and anthracyclines [28]. Small phase II studies generally report response rates of 18-100%, but most responses are transient. One randomized trial comparing chemotherapy (+TSEB) to topical therapy, showed no benefit for the more intensive approach [29]. For these reasons chemotherapy is generally reserved for patients with evidence of large cell transformation or extensive nodal or visceral disease and that has become refractory to all other modalities.

9. New Agents

There are multiple new agents that have shown efficacy in patients with advanced CTCL in phase II clinical trials. **Alemtuzumab** (Campath®) is a monoclonal anti CD52 antibody that has been shown to have efficacy in several types of lymphomas including T-cell lymphomas. In phase II trials of advanced/refractory CTCL patients the response rates have been variable (30-85%), however most responses are short lived. Furthermore there is a significant toxicity profile especially in heavily pretreated patients, however there may be a role for low-dose intermittent subcutaneous Alemtuzumab. Currently Alemtuzumab is not approved for CTCL in Canada therefore we only consider Alemtuzumab in the setting of a clinical trial [30-32]. Histone deacetylase inhibitors such as Vorinostat® (suberoylanilide hydroxamic acid; SAHA) have also shown efficacy in phase II clinical trails with response rates of 30% in heavily pretreated patients (50). Vorinostat® is currently FDA approved in the USA for advanced CTCL patients, however it is not currently available in Canada. Other agents that have shown efficacy in small phase II clinical trials include **Bortezomib** (Velcade®) and **Interleukin 12,** and studies are ongoing [33, 34].

Recommendations by Stage

Ia-Limited Patches/Plaques

The largest group of presenting patients has stage Ia disease. These patients generally have indolent disease and may be managed conservatively. Asymptomatic patients can be observed without therapy, as there is no evidence treatment alters the natural history of the disease. Patients with limited, but symptomatic disease may be treated with topical corticosteroids or a combination of topical imiquimod and topical retinoids. Imiquimod is typically applied in a thin layer to affected areas three times a week. We suggest application during the day monitoring for reaction (erythema is very common). If no minimal reaction is noted application can be switched to nightly. Tazarotene three times per week the morning after imiquimod can be added if there has had suboptimal response to imiquimod alone. Topical immunotherapy should be **used with caution** if applied while light therapy is being delivered as skin reaction may be heightened. Phototherapies with PUVA or NB-UVB are also alternatives if topical therapies are too cumbersome or ineffective. For patients with small areas of localized disease refractory to topical therapy, involved field radiation is also a very effective treatment [12].

Ib-Disseminated Patches/Plaques

Patients with more extensive patches or plaques that cover at least 10% of the skin surface area will generally be symptomatic and should be offered therapy. Phototherapy (PUVA or NB-UVB) will be used as first-line therapy in the majority of patients. Patients who have inadequate response to phototherapy should have systemic immunotherapy added to their treatment with Interferon-Apha +/- oral retinoids. Patients who fail combination immuno/phototherapy or who have very extensive thick plaques should be referred to the Hamilton Juravinski Cancer Centre Radiation Oncology Department for an opinion regarding TSEB [12].

Patients with skin tumours (T3) or lymph node involvement (N1 or LN 2-4)

Skin tumours can be treated with radiation therapy. This will generally consist of involved field irradiation to individual deep lesions. Patients with extensive skin involvement should be offered TSEB. Patients with enlarged nodes should receive involved field radiation (**800 cGy/1-2500 cGy/10 fractions**) in addition to any skin-based therapy. Tumour stage MF typically has a poorer prognosis than earlier stage skin lesions, therefore these patients should be considered for combination immunotherapy with Interferon alpha +/- oral retinoids [12].

Erythroderma (also see Sézary Syndrome)

Patients with advanced skin disease (erythrodermic-CTCL) have a poor prognosis. Patients should receive TSEB. This will typically induce remissions including healing of necrotic ulcers. Patients who are B0 may experience excellent long-term control (at least 35% 10-year progression-free survival) with TSEB as monotherapy. Patients who are B1 (E-CTCL or Sézary Syndrome, see separate section) should be referred for ECP in conjunction with TSEB [35]. ECP is currently available at the University Health Network in Toronto. Given the poorer prognosis of patients with total body erythroderma or blood involvement, these patients should also be managed with immunotherapy with Interferon alpha +/- oral retinoids in combination with skin targeted therapies [36, 37]. Patients progressing on combined immunotherapy and TSEB should be considered for systemic chemotherapy.

Visceral Involvement

Patients with visceral involvement have much more aggressive disease with median survivals usually less than 2 years. If there is no evidence of large cell transformation, these patients should be initiated on therapy with a combination of Interferon alpha, oral retinoids and TSEB or PUVA based on the degree of skin involvement. If patients progress on combination therapy they should be treated with systemic chemotherapy. Fludarabine is used as first-line therapy in most cases. If patients have a documented large cell transformation of their disease they should be offered anthracycline-based chemotherapy such as CHOP. Patients eligible for intensive therapy such as allogeneic stem cell transplantation who have good cardiac function may also be treated with CHOP as remissions may be induced faster [38]. Remissions with most regimens are reported to be short-lived.

Role of Radiation in Advanced Disease

Low-dose local or local/regional radiation can be very effective in palliating symptoms and prolonging survival due to organ compromise, particularly in the CNS, lung, eye or orbit. Patients who have isolated visceral involvement and who are receiving more aggressive topical management to skin disease may be considered for more aggressive systemic therapy, and more aggressive IF-XRT to the known site of metastasis. Targeted or low dose TSEB therapy is also very useful in the palliation of difficult skin symptoms especially pruritis.

Mycosis Fungoides Variants

Many variants of mycosis fungoides have been reported, but most have clinical behaviors similar to MF. The WHO recognizes 3 distinct variants: MF-Associated follicular mucinosis, pagetoid reticulosis, and granulomatous slack skin.

Folliculotropic MF is a distinct variant characterized by the presence of folliculotropic infiltrates with sparing of the epidermis, mucinous degeneration of the hair follicles and preferential involvement of the head and neck area. Atypical cells are found primarily in the perivascular and periadnexal location of the dermis, usually sparing the epidermis. The malignant T-cells have a similar phenotype to classic MF. This entity has a somewhat worse prognosis than classical MF and is less responsive to skin-targeted therapies as the atypical lymphocytes tend to be deeper in the skin than classic MF. Total skin electron beam therapy is the preferred option in such cases [1].

Pagetoid reticulosis is characterized by the presence of localized patches or plaques with an intraepidermal proliferation of neoplastic T-cells. The malignant T-cells can be either CD4+ or CD8+, and CD30 can also be expressed. It is localized and does not disseminate beyond the skin. Therapy should be conservative with excision or local radiation. Long-term survival approaches 100% [1].

Granulomatous slack skin is a rare lymphoproliferative disease generally regarded as a variant of mycosis fungoides. It may, however, be seen in association with other types of lymphoma including classical MF and Hodgkin's disease. Patients typically slowly develop pendulous folds of atrophic skin, preferentially involving the axilla or groin. Morphology generally consists of a granulomatous infiltrate of atypical CD4+ T-lymphocytes admixed with macrophages. Treatment is individualized as there is little experience with this MF subtype, however radiation to localized areas is typically part of the treatment algorithm [39].

Transformation

Patients with tumour stage disease can often have elements of large cell transformation on biopsy specimens with emergence of larger malignant cells (> + 4 x = times the size of a small lymphocyte) that can also express CD30. It is often difficult to determine when a tumour sample has progressed to true large cell peripheral T-cell lymphoma requiring aggressive chemotherapy, however in general if a tumour has greater than 25 % large cells or sheets of large cells then consideration should be given to aggressive transformation [4].

Sézary Syndrome

Diagnosis

Sézary syndrome is defined as the triad of erythroderma, generalized lymphadenopathy and the presence of neoplastic T-cells (Sézary cells) in skin, lymph nodes and peripheral blood. Some investigators allow for less than 90% of the skin to be erythrodermic (even less than 25%), or require the presence of general symptoms (e.g. thermoregulatory difficulties), in order to designate a patient as having Sézary syndrome. Despite this being a severe and widespread manifestation of CTCL, skin biopsies (the hallmark of diagnosis) are often

more consistent with dermatitis than CTCL. Clinical suspicion is very important and non-diagnostic biopsies should never misdirect investigations. Recently, there has been an attempt to separate out those patients with E-CTCL and those with Sézary syndrome, for end reporting, management, and research purposes. The histologic features of Sézary syndrome may be similar to those in mycosis fungoides; however, the cellular infiltrates are more often monotonous and epidermotropism may sometimes be absent. Involved lymph nodes characteristically show a dense, monotonous infiltrate of Sézary cells with effacement of the normal nodal architecture. The tumor cells are $CD3^+$, $CD4^+$, $CD45RO^+$, $CD8^-$ and CD30-, with loss of CD7 and CD26. There is no consensus regarding the degree of peripheral blood involvement required to make a diagnosis, however, we will use the commonly used cut-off of 1 x 10^9/L or 5% Sézary cells. Some experts consider a CD4:CD8 ratio of greater than 10 (normal <3) to be more specific than the Sézary cell count [4, 6, 39].

Baseline Investigations

Patients with Sézary syndrome should have a biopsy of the skin and affected lymph nodes as well as chest x-ray and abdominal CT or ultrasound. Peripheral blood film and bone marrow biopsy should be performed. Flow cytometry of peripheral blood should also be performed to quantify as well as characterize peripheral blood involvement.

Prognosis

The prognosis of Sézary syndrome is very poor, and the survival may be as low as 11% at 5 years [1], though some reports indicate that it may be as great as 40-50% [35].

Treatment

Patients with Sézary Syndrome should be referred for ECP in conjunction with TSEB and Interferon alpha +/- oral retinoids [35, 40-42]. Patients progressing on combination therapy should be considered for systemic chemotherapy.

Lymphomatoid Papulosis

Diagnosis

Lymphomatoid papulosis (LyP) is a chronic, recurrent, self-healing papulonodular skin eruption with histologic features of a lymphoma. The histologic features are extremely variable with variable numbers of large $CD30^+$ cells, small lymphocytes and inflammatory histiocytes, however there are 3 subtypes recognized.

- **T**ype A lesions are characterized by scattered large Reid Sternberg like CD30+ cells surrounded by a mixed inflammatory infiltrate.
- Type B lesions have a predominance of atypical cerebriform lymphocytes with minimal inflammatory infiltrate. The epidermotropism of MF is not typically seen.
- Type C lesions are considered borderline lesions and in a spectrum with anaplastic lymphoma of the skin. Typically there are > 75% large atypical CD30+ cells. Subcutaneous fat is generally spared.

Lymphomatoid papulosis and anaplastic large cell lymphoma may be difficult to distinguish histologically. The clinical history of relapsing and remitting lesions is important. Clonal T-cell receptor gene rearrangements are not consistently found in LyP. The majority of type B lesions are clonally restricted, however most type A lesions are not [39, 43].

Prognosis

The 5-year survival of patients with lymphomatoid papulosis is 100%. Patients with LyP have been noted to have secondary lymphoid malignancies such as MF, Hodgkin's or cutaneous anaplastic large cell lymphoma. These can be coincident, predate or postdate the diagnosis of LyP [1].

Treatment

There is no curative therapy. Patients with small bulk asymptomatic disease may be managed with observation alone. Symptomatic patients should be offered involved field radiotherapy if lesions are localized or oral methotrexate. Methotrexate is typically started at a dose of 10-15 mg PO weekly and may be escalated to a maximum of 30 mg weekly. Patients with LyP typically respond less well to topical nitrogen mustard or PUVA. Systemic chemotherapy is not needed unless ALCL is diagnosed.

Cutaneous Lymphomas other than MF/SS/LyP

Non MF/SS cutaneous lymphomas are also a heterogeneous group of disorders, however they have very different pathophysiology than MF/SS, therefore the ISCL has recently derived a distinct staging system for non MF/SS cutaneous lymphomas. The staging system differs most with respect to quantifying the degree of skin involvement, which would impact choice of therapy for non MF/SS skin lymphoma patients [5].

Table 8.

ISCL/EORTC Proposal on TNM Classification of Cutaneous Lymphoma Other Than MF/SS

Classification
T
T1: Solitary skin involvement
T1a: a solitary lesion <5 cm diameter
T1b: a solitary >5 cm diameter
T2: Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions*
T2a: all-disease-encompassing in a <15-cm-diameter circular area
T2b: all-disease-encompassing in a >15- and <30-cm-diameter circular area
T2c: all-disease-encompassing in a >30-cm-diameter circular area
T3: Generalized skin involvement
T3a: multiple lesions involving 2 noncontiguous body regions
T3b: multiple lesions involving >=3 body regions
N
N0: No clinical or pathologic lymph node involvement
N1: Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement
N2: Involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region† that does not drain an area of current or prior skin involvement
N3: Involvement of central lymph nodes
M
M0: No evidence of extracutaneous non–lymph node disease
M1: Extracutaneous non–lymph node disease present

*Definition of body regions: Head and neck: inferior border—superior border of clavicles, T1 spinous process. Chest: superior border—superior border of clavicles; inferior border—inferior margin of rib cage; lateral borders—mid-axillary lines, glenohumeral joints (inclusive of axillae). Abdomen/genital: superior border—inferior margin of rib cage; inferior border—inguinal folds, anterior perineum; lateral borders—mid-axillary lines. Upper back: superior border—T1 spinous process; inferior border—inferior margin of rib cage; lateral

borders—mid-axillary lines. Lower back/buttocks: superior border—inferior margin of rib cage; inferior border—inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders—mid-axillary lines. Each upper arm: superior borders—glenohumeral joints (exclusive of axillae); inferior borders—ulnar/radial-humeral (elbow) joint. Each lower arm/hand: superior borders—ulnar/radial-humeral (elbow) joint. Each upper leg (thigh): superior borders—inguinal folds, inferior gluteal folds; inferior borders—mid-patellae, mid-popliteal fossae. Each lower leg/foot: superior borders—mid-patellae, mid-popliteal fossae.

[†]Definition of lymph node regions is consistent with the Ann Arbor system: Peripheral sites: antecubital, cervical, supraclavicular, axillary, inguinal-femoral, and popliteal. Central sites: mediastinal, pulmonary hilar, paraortic, iliac.

Baseline Investigations

All non-MF/SS cutaneous lymphoma patients require investigations at baseline to ensure the absence of systemic disease.

- Thorough history and physical examination
- Mapping of skin lesions
- CBC, differential, & blood film
- Liver function tests, calcium profile, renal profile, LDH
- CT scan of chest, abdomen, and pelvis
- Biopsy of enlarged lymph nodes
- Bone marrow aspirate and biopsy

Primary Cutaneous CD30+ T-cell Lymphoma/Anaplastic Large cell lymphoma of the Skin

Diagnosis

$CD30^+$ large T-cell/anaplastic lymphoma of skin consists of large tumor cells, the majority of which express CD30 antigen. There must be no evidence or history of lymphomatoid papulosis, mycosis fungoides or systemic lymphoma. These lymphomas tend to occur in adults as solitary or localized nodules or tumors that may regress spontaneously in up to 25% of cases. Histology typically reveals large anaplastic cells, however pleomorphic or immunoblastic cells are also described. Cells are typically CD4+, (only 5% are CD8+) with loss of CD2, CD5 and or CD3. It is often difficult to differentiate systemic from cutaneous anaplastic large cell lymphoma, however cutaneous ALCL typically expresses cutaneous lymphocyte antigen (CLA), but not epithelial membrane antigen (EMA) or ALK typically seen in systemic ALCL [6, 39].

Baseline Investigations

All patients should have a CBC, blood film, serum electrolytes, LDH, and liver function testing as well as a CT scan of the chest, abdomen and pelvis, and bone marrow biopsy. Patients with visceral/nodal or bone marrow involvement should be considered to have systemic anaplastic large cell lymphoma **(see T-cell Lymphomas)**.

Treatment

The prognosis of this condition is very favorable with a 5-year survival of 95% [1, 2]. Patients with solitary or localized skin lesions should be treated with local radiation. Patients with more generalized skin lesions should be treated with 3-6 cycles of CHOP chemotherapy with or without radiation. Patients who recur in the skin continue to have a good prognosis and may be managed with further local therapy.

❖❖❖❖❖

Peripheral T-Cell Lymphoma, Unspecified (NOS) ❖

Diagnosis

Peripheral T-cell lymphoma, unspecified, in the WHO classification is a very heterogenous group of diseases [6]. These must be distinguished from mycosis fungoides not only morphologically, but also on the basis of clinical presentation.

Peripheral T-cell lymphoma unspecified has been provisionally categorized into the following entities:

- Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma
- Cutaneous gamma/delta T-cell lymphoma
- Primary cutaneous CD4+ small/medium sized pleomorphic T-cell lymphoma
- Primary cutaneous T-cell lymphoma, unspecified

Distinguishing these entities from each other and from atypical mycosis fungoides requires review of generous and preferably multiple skin biopsies with immunophenotypic studies. The typical features of each are well summarized in the WHO-EORTC classification paper [6].

Baseline Investigations

An aggressive search for systemic lymphoma is essential as many of these patients have or will develop disseminated disease. All patients should have a CT scan of the chest, abdomen and pelvis, CBC, electrolytes, liver function tests, LDH, blood film and bone marrow biopsy.

Prognosis and Treatment

Patients with clinical or pathologic features suggestive of MF will be considered to have MF and will be treated as MF. The prognosis and treatment differs for the different entities:

Primary cutaneous aggressive epidermotropic CD8⁺ cytotoxic T-cell lymphoma: These lymphomas are thought to be aggressive with a median survival of less than 3 years, whether they are large cell or small cell morphology [44]. Patients will typically be treated with CHOP x 6-8 cycles, but should be advised that this is not considered curative treatment. Symptomatic therapy is a reasonable approach for patients not considered eligible for more intensive treatment

Cutaneous gamma/delta T-cell lymphoma: Prognosis of this group is felt to be even worse, with median survival in a small series of only 15 months [45]. CHOP is our standard therapy for patients felt able to tolerate this therapy. Symptomatic therapy is a reasonable approach for other patients.

Primary cutaneous CD4⁺ small/medium sized pleomorphic T-cell lymphoma: This entity is felt to have a relatively favorable prognosis, with reported 5-year survivals of 60-80% [46]. Patients with localized disease will typically be treated with surgical excision or involved field radiation [6]. Patients with more generalized disease should receive oral alkylating agents such as cyclophosphamide or Interferon alpha.

Primary cutaneous T-cell lymphoma, unspecified: Prognosis for this group is felt to be poor with 5-year survival rates of < 20% [6]. CHOP will be standard therapy for most patients, with symptomatic therapy for patients felt to be unable to tolerate aggressive therapy.

Subcutaneous Panniculitis-Like T-Cell Lymphoma

Diagnosis

Patients with subcutaneous panniculitis-like T-cell lymphoma typically present with multiple subcutaneous nodules usually in the absence of other sites of disease. Some patients may present with a hemophagocytic syndrome with pancytopenia, fever, and hepatosplenomegaly. On biopsy, an infiltrate typically extends through the subcutaneous tissue. The overlying dermis and epidermis are typically uninvolved. A helpful finding is ringing of the neoplastic cells around the individual fat cells (angiocentricity). There two subtypes of SPLTCL, α/β usually expressing CD8 or γ/δ which is typically CD4- and CD8- but CD56+ [6, 39].

Baseline Investigations

Patients should have CT scans of chest, abdomen and pelvis and bone marrow biopsies to rule out dissemination. Patients should also have routine chemistry including CBC, LDH, renal profile, liver profile coagulation profile and calcium profile.

Treatment & Survival

Prognosis with this lymphoma has previously been reported to be very poor, but more recent reports suggest better outcome. Patients with the $CD8^+$ α/β T-cell phenotype typically have a protracted clinical course with recurrent subcutaneous lesions, but without extracutaneous dissemination. Five-year survival of more than 80% is now reported. However patients with the CD56+ γ/δ can have a much more aggressive clinical course (**see peripheral T cell lymphoma of the skin**) [6, 47].

Standard therapy in our Centre will be CHOP x 6-8 cycles. It should be noted that recent reports suggest selected patients may be controlled for long periods of time with corticosteroids alone.

Acute T-cell Leukemia/Lymphoma (ATLL)

Acute T-cell leukemia/lymphoma is an aggressive neoplasm associated with infection with the HTLV-I virus. Most patients with skin involvement have widely disseminated disease, however, some patients with the smouldering variant may only have skin lesions [6, 36]. Our policy regarding management of this disease is summarized in the **T-cell Lymphoma Section**. Patients with skin only involvement may be treated with skin-targeted therapies as used in MF.

Extranodal NK/T-cell Lymphoma, Nasal Type

This lymphoma commonly affects the nasopharynx, but the skin is the second most common site of involvement and may be the sole site of involvement. Patients should be treated similarly to those with extracutaneous disease **(see T-cell Lymphoma Section).**

Blastic NK-cell Lymphoma

This rare entity is aggressive with a poor prognosis and only short responses to chemotherapy (**see T-cell Lymphoma Section)**.

B-Cell Lymphomas

1. Follicular Lymphoma
2. Marginal Zone B-Cell Lymphoma
3. Diffuse Large B-Cell Lymphoma

1. Follicular Lymphoma

Diagnosis

Follicular lymphoma is a tumor composed of follicle center cells, usually a mixture of large and small-cleaved follicle center cells and centroblasts (large follicle center cells with prominent nucleoli) typically in nodular or diffuse infiltrates, with the almost constant sparing of the epidermis. The neoplastic cells mark as B-cells and express CD19, CD20, CD22, CD79a and do not express CD5 or CD10 [1].

Baseline Investigations

Patients should have CT scans of chest, abdomen and pelvis as well as a bone marrow biopsy to rule out disseminated disease. Patients with nodal/visceral disease should be managed as systemic disease **(see Follicular Lymphoma Section)**.

Prognosis

The 5-year survival of these patients is 95% [1].

Treatment

Most patients present with localized disease and should be treated with involved field radiation **(2500-3500 cGy in 10-20 fractions)** [37]. Systemic chemotherapy should be considered in generalized skin lesions or extracutaneous dissemination [48]. Where available patients should be entered into clinical trials. Patients with follicular low-grade lesions (follicle center cell grade I-II) who require chemotherapy should be treated with chlorambucil (0.07 mg/kg/day) +/-rituximab. Patients with localized grade III follicle center cell lesions will also receive radiation alone, while those with more extensive disease should be treated with 3-6 cycles of CHOP-rituximab and involved field radiation.

2. Marginal Zone B-Cell Lymphoma

These lymphomas are characterized by a proliferation of small lymphocytes, lymphoplasmacytoid cells, and plasma cells. In the central areas of the infiltrates variable numbers of reactive T-cells, small $CD20^+$ B-cells and in many cases reactive follicular structures may be observed. A significant minority of cases have been associated with Borrelia burgdorferi infection which should be treated before considering alternative lymphoma therapies [1].

Baseline Investigations

Patients should have CT scans of chest, abdomen and pelvis as well as a bone marrow biopsy to rule out disseminated disease.

Prognosis

The 5-year survival approaches 100%.

Treatment

Because of the indolent nature of these lesions patients with asymptomatic small bulk lesions can be observed without treatment. Patients requiring therapy for localized disease should be treated with local radiotherapy **(2500-3500 cGy in 10-20 fractions)**. Chemotherapy with chlorambucil or CVP +/- rituximab should be reserved for more extensive disease.

3. Diffuse Large B-Cell Lymphoma

Diagnosis

The WHO-EORTC classification recognizes three distinct aggressive B-cell skin lymphomas:

- Primary cutaneous large B cell lymphoma (PCLBCL)-leg type,
- PCLBCL-other, and
- Intravascular large B-cell lymphoma [6].

Prognosis & Treatment

PCLBCL-leg type typically affects older women [49]. The prognosis of this subtype is controversial, but may be better than comparably staged nodal disease. Patients are typically treated with 3-6 cycles of CHOP-rituximab and involved field irradiation. Patients with PCLBCL-other are felt to have an excellent prognosis and are treated with CHOP-rituximab and involved field irradiation, though patients not felt to be candidates for anthracycline-based chemotherapy may do very well with conservative management. Intravascular B-cell lymphoma of skin has a less favorable prognosis, but typically does better than patients with this subtype arising in other sites (lungs, CNS, etc). Most patients will be treated with CHOP-rituximab and involved filed irradiation.

References

1. Willemze, R., et al., *EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer*. Blood, 1997. **90**(1): p. 354-71.
2. Beljaards, R.C., et al., *Prognostic significance of CD30 (Ki-1/Ber-H2) expression in primary cutaneous large-cell lymphomas of T-cell origin. A clinicopathologic and immunohistochemical study in 20 patients.* Am J Pathol, 1989. **135**(6): p. 1169-78.
3. Willemze, R., et al., *Diffuse large cell lymphomas of follicular center cell origin presenting in the skin. A clinicopathologic and immunologic study of 16 patients.* Am J Pathol, 1987. **126**(2): p. 325-33.
4. Olsen, E., et al., *Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC).* Blood, 2007. **110**(6): p. 1713-22.
5. Kim, Y.H., et al., *TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas*

(ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood, 2007. **110**(2): p. 479-84.
6. Willemze, R., et al., *WHO-EORTC classification for cutaneous lymphomas.* Blood, 2005. **105**(10): p. 3768-85.
7. Sausville, E.A., et al., *Histologic assessment of lymph nodes in mycosis fungoides/Sézary syndrome (cutaneous T-cell lymphoma): clinical correlations and prognostic import of a new classification system.* Hum Pathol, 1985. **16**(11): p. 1098-109.
8. Demierre, M.F., F.M. Foss, and H.K. Koh, *Proceedings of the International Consensus Conference on Cutaneous T- cell Lymphoma (CTCL) Treatment Recommendations. Boston, Massachusetts, Oct. 1 and 2, 1994.* J Am Acad Dermatol, 1997. **36**(3 Pt 1): p. 460-6.
9. Diamandidou, E., P.R. Cohen, and R. Kurzrock, *Mycosis fungoides and Sézary syndrome.* Blood, 1996. **88**(7): p. 2385-409.
10. Jones, G.W., et al., *Total skin electron radiation in the management of mycosis fungoides: Consensus of the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Project Group.* J Am Acad Dermatol, 2002. **47**(3): p. 364-70.
11. Zackheim, H.S., et al., *Prognosis in cutaneous T-cell lymphoma by skin stage: long-term survival in 489 patients.* J Am Acad Dermatol, 1999. **40**(3): p. 418-25.
12. Trautinger, F., et al., *EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome.* Eur J Cancer, 2006. **42**(8): p. 1014-30.
13. Zackheim, H.S., *Treatment of patch-stage mycosis fungoides with topical corticosteroids.* Dermatol Ther, 2003. **16**(4): p. 283-7.
14. Heald, P., et al., *Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial.* J Am Acad Dermatol, 2003. **49**(5): p. 801-15.
15. Deeths, M.J., et al., *Treatment of patch and plaque stage mycosis fungoides with imiquimod 5% cream.* J Am Acad Dermatol, 2005. **52**(2): p. 275-80.
16. Haserick, J., J. Richardson, and D.J. Grant, *Remission of lesions in mycosis fungoides following topical application of nitrogen mustard.* Cleve Clin Q, 1959. **26**: p. 144-147.
17. Kim, Y.H., *Management with topical nitrogen mustard in mycosis fungoides.* Dermatol Ther, 2003. **16**(4): p. 288-98.
18. Zhang, C. and M. Duvic, *Retinoids: therapeutic applications and mechanisms of action in cutaneous T-cell lymphoma.* Dermatol Ther, 2003. **16**(4): p. 322-30.
19. Duvic, M., et al., *Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results.* J Clin Oncol, 2001. **19**(9): p. 2456-71.
20. Trent, J.T., P. Romanelli, and F.A. Kerdel, *Topical Targretin and intralesional interferon alfa for cutaneous lymphoma of the scalp.* Arch Dermatol, 2002. **138**(11): p. 1421-3.
21. Baron, E.D. and S.R. Stevens, *Phototherapy for cutaneous T-cell lymphoma.* Dermatol Ther, 2003. **16**(4): p. 303-10.
22. Stern, R.S., *Genital tumors among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. The Photochemotherapy Follow-up Study.* N Engl J Med, 1990. **322**(16): p. 1093-7.
23. Stern, R.S., K.T. Nichols, and L.H. Vakeva, *Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). The PUVA Follow-Up Study.* N Engl J Med, 1997. **336**(15): p. 1041-5.
24. Olsen, E.A., *Interferon in the treatment of cutaneous T-cell lymphoma.* Dermatol Ther, 2003. **16**(4): p. 311-21.
25. Rupoli, S., et al., *Long-term experience with low-dose interferon-alpha and PUVA in the management of early mycosis fungoides.* Eur J Haematol, 2005. **75**(2): p. 136-45.
26. Hoppe, R.T., *Mycosis fungoides: radiation therapy.* Dermatol Ther, 2003. **16**(4): p. 347-54.
27. Zic, J.A., *The treatment of cutaneous T-cell lymphoma with photopheresis.* Dermatol Ther, 2003. **16**(4): p. 337-46.
28. Kuzel, T.M., *Systemic chemotherapy for the treatment of mycosis fungoides and Sézary syndrome.* Dermatol Ther, 2003. **16**(4): p. 355-61.
29. Kaye, F.J., et al., *A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides.* N Engl J Med, 1989. **321**(26): p. 1784-90.

30. Kennedy, G.A., et al., *Treatment of patients with advanced mycosis fungoides and Sézary syndrome with alemtuzumab.* Eur J Haematol, 2003. **71**(4): p. 250-6.
31. Lundin, J., et al., *Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sézary syndrome.* Blood, 2003. **101**(11): p. 4267-72.
32. Bernengo, M.G., et al., *Low-dose intermittent alemtuzumab in the treatment of Sézary syndrome: clinical and immunologic findings in 14 patients.* Haematologica, 2007. **92**(6): p. 784-94.
33. Zinzani, P.L., et al., *Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma.* J Clin Oncol, 2007. **25**(27): p. 4293-7.
34. Duvic, M., et al., *A phase II open-label study of recombinant human interleukin-12 in patients with stage IA, IB, or IIA mycosis fungoides.* J Am Acad Dermatol, 2006. **55**(5): p. 807-13.
35. Wilson, L., et al., *Experience with total skin electron beam therapy in combination with extracorporeal photopheresis in the management of patients with erythrodermic (T4) mycosis fungoides.* J Am Acad Dermatol, 2000. **43**(1 Pt 1): p. 54-60.
36. Setoyama, M., Y. Katahira, and T. Kanzaki, *Clinicopathologic analysis of 124 cases of adult T-cell leukemia/lymphoma with cutaneous manifestations: the smouldering type with skin manifestations has a poorer prognosis than previously thought.* J Dermatol, 1999. **26**(12): p. 785-90.
37. Piccinno, R., et al., *Radiotherapy of cutaneous B cell lymphomas: our experience in 31 cases.* Int J Radiat Oncol Biol Phys, 1993. **27**(2): p. 385-9.
38. Molina, A., et al., *Durable clinical, cytogenetic, and molecular remissions after allogeneic hematopoietic cell transplantation for refractory Sézary syndrome and mycosis fungoides.* J Clin Oncol, 2005. **23**(25): p. 6163-71.
39. Jaffe, E., et al., *World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of Haematopoietic and Lymphoid Tissues.* 2001, Lyon: IARC Press.
40. Ross, C., et al., *Interferon treatment of cutaneous T-cell lymphoma.* Eur J Haematol, 1993. **51**(2): p. 63-72.
41. Olsen, E.A. and P.A. Bunn, *Interferon in the treatment of cutaneous T-cell lymphoma.* Hematol Oncol Clin North Am, 1995. **9**(5): p. 1089-107.
42. Richardson, S.K., et al., *High clinical response rate with multimodality immunomodulatory therapy for Sézary syndrome.* Clin Lymphoma Myeloma, 2006. **7**(3): p. 226-32.
43. Liu, H.L., et al., *CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma.* J Am Acad Dermatol, 2003. **49**(6): p. 1049-58.
44. Berti, E., et al., *Primary cutaneous CD8-positive epidermotropic cytotoxic T cell lymphomas. A distinct clinicopathological entity with an aggressive clinical behavior.* Am J Pathol, 1999. **155**(2): p. 483-92.
45. Toro, J.R., et al., *Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma.* Blood, 2003. **101**(9): p. 3407-12.
46. Bekkenk, M.W., et al., *Peripheral T-cell lymphomas unspecified presenting in the skin: analysis of prognostic factors in a group of 82 patients.* Blood, 2003. **102**(6): p. 2213-9.
47. Hoque, S.R., et al., *Subcutaneous panniculitis-like T-cell lymphoma: a clinicopathological, immunophenotypic and molecular analysis of six patients.* Br J Dermatol, 2003. **148**(3): p. 516-25.
48. Rijlaarsdam, J.U., et al., *Treatment of primary cutaneous B-cell lymphomas of follicle center cell origin: a clinical follow-up study of 55 patients treated with radiotherapy or polychemotherapy.* J Clin Oncol, 1996. **14**(2): p. 549-55.
49. Goodlad, J.R., et al., *Primary cutaneous diffuse large B-cell lymphoma: prognostic significance of clinicopathological subtypes.* Am J Surg Pathol, 2003. **27**(12): p. 1538-45.