Cutaneous T-Cell Lymphomas: A Review With Emphasis on New Treatment Approaches

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Primary cutaneous T-cell lymphomas represent a wide variety of non-Hodgkin lymphomas that are characterized by a distinct clinical presentation. Advanced molecular and biological techniques have enhanced the recognition of cutaneous T-cell lymphomas. The most common subtypes of cutaneous T-cell lymphomas are the epidermotropic variants mycosis fungoides and Sézary syndrome. At present, a stage-adjusted therapy is the best concept available, since early aggressive treatment options did not improve the prognosis of patients with cutaneous T-cell lymphomas. Accurate diagnostic and clinical assessment as well as identification of prognostic factors provides a helpful basis for treatment strategies. Current medical literature on diagnosis, prognosis, and treatment is reviewed with emphasis on new biologic response-modifying treatment options.

PRIMARY CUTANEOUS T-cell lymphomas (CTCL) represent a heterogeneous group of lymphomas with a distinct clinical presentation, behaviour, and prognosis. Most classification systems were designed for non-Hodgkin lymphomas and do not provide a helpful characterization of cutaneous lymphomas. In 1997, the European Organization for Research and Treatment of Cancer (EORTC) presented its own clinically oriented classification of primary cutaneous lymphomas taking into account the histological and molecular features.[1] Although for pathology reporting many pathologists prefer the currently developed scheme of the World Health Organization (WHO), the EORTC classification still carries major clinical and therapeutical implications (Table 1).[2]

Mycosis fungoides (MF) and Sézary syndrome (SS) are by far the most common types of CTCL in the general population comprising 50% of CTCL. Other, less common variants of CTCL include the CD30-positive lymphoproliferative disorders, CD30-negative large T-cell lymphoma, pleomorphic T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and granulomatous slack skin.

The origin of CTCL is poorly understood as viral and retroviral theories have not been conclusive to date, whereas the process of chronic antigenic stimulation remains possible. Studies of the cutaneous lymphocyte antigen (CLA), chemokines, and cell adhesion receptors have provided new insights into skin homing mechanisms, which play a role in cutaneous T-cell lymphomas.[3] It is believed that the process of T-lymphocytes homing to the skin is mediated by the CLA, which is a ligand for E-selectin. E-selectin exhibit selective lymphocyte-binding properties and is present on the cutaneous endothelial cells.[4] Other regulating skin homing receptors include intracellular adhesion molecule 1 (ICAM-1) with its ligand leukocyte function antigen (LFA-1) and the recently described chemokine receptor CCR4 and its ligand TARC (thymus and activation regulated chemokine).[5]

While the underlying molecular pathogenesis remains unknown, but in its early stages MF is thought to develop from skin homing T-lymphocytes that accumulate because of defective apoptosis and in some cases progress into a true neoplasm. Recently published data of oncogene abnormalities in CTCL variants demonstrate decreased *Fas* expression on peripheral malignant $CD4^+$T-lymphocytes indicating an impaired *Fas*-mediated T-cell apoptosis.[6] Additional studies on

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Table 1. EORTC Classification for Primary Cutaneous T-cell Lymphomas and Corresponding Categories in the WHO Classification

EORTC	WHO
Cutaneous T-cell Lymphoma	
Indolent	
Mycosis fungoides	Mycosis fungoides
Mycosis fungoides variants	Mycosis fungoides variants
Follicular MF	Follicular MF
Pagetoid reticulosis	Pagetoid reticulosis
$CD30^+$ large T-cell lymphoma	Primary cutaneous $CD30^+$ ALCL ($CD30^+$ lymphoproliferative diseases including lymphomatoid papulosis)
Lymphomatoid Papulosis	
Aggressive	
Sézary syndrome	Sézary syndrome
$CD30^-$ large T-cell lymphoma	Peripheral T-cell lymphoma, unspecified
Provisional entities	
CTCL, pleomorphic, small/ medium-sized	Peripheral T-cell lymphoma, unspecified
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
Granulomatous slack skin	Granulomatous slack skin

molecular pathogenesis identify a consistent upregulation of *JUN-B* in CTCL variants, suggesting this gene plays a critical role in pathogenesis of CTCL.[7]

Following the EORTC classification scheme, we present a review of the distinct entities of primary CTCL with emphasis on new treatment options.

MYCOSIS FUNGOIDES/SEZARY SYNDROME

MF is the most common form of CTCL with a male predominance of approximately 2:1 and a predominance of patients of African descent about 1.6:1. It has a yearly incidence of 0.36 cases per 100,000 of the population that has remained constant over the last decade.[8] However, an increasing number of cases in children are reported. MF, was first described by Alibert in the 19th century, due to the mushroom-like appearance of tumors. It is classified as an indolent lymphoma by the EORTC.[9] Sézary syndrome is the leukemic and more aggressive variant of CTCL, which is characterized by circulating, atypical, malignant T-lymphocytes with cerebriform nuclei (Sézary cells), the presence of erythroderma, disabling pruritus, keratoderma, and lymphadenopathy (Fig 1). The recommended staging system is in according to the TNMB (tumor, node, metastasis, blood) classification that is based by multivariate prognostic studies (Tables 2 and 3).

Clinically, MF is typified by the development of patches, plaques, or tumors (Figs 2 and 3). In early stages, it might resemble eczematous dermatitis, psoriasis, or parapsoriasis. Varied subtypes have been described including granulomatous, hypopigmented, bullous, pustular, hyperkeratotic MF, and MF-associated follicular mucinosis, with or without alopecia. The d'emblée presentation is defined by *de novo* appearance of tumors. Pagetoid reticulosis is a rare and controversial variant that presents with acral verrucous lesions with large epidermotropic lymphocytes and a benign prognosis.

Microscopic assessment is required for diagnosis. Characteristic histologic features are a papillary dermal band-like infiltrate with small to medium-sized lymphocytes with hyperchromatic, hyperconvoluted nuclei, and variable findings of inflammatory cells. Epidermal exocytosis is classic (Fig 4). Pautrier's microabscesses are considered to be characteristic findings, but seen infrequently. Tumor lesions express more diffuse, superficial, and deep infiltrates with diminished epidermotropism.[10]

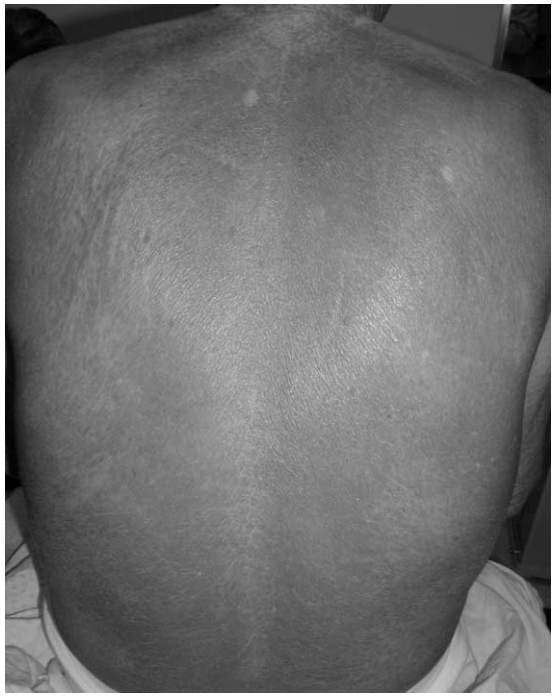

Fig 1. Sézary syndrome with generalized erythroderma.

Table 2. TNMB Classification for MF/SS

T (skin)	
T1	Limited patch/plaque (<10% of BSA)
T2	Generalized patch/plaque(>10% of BSA)
T3	Tumors
T4	Generalized erythroderma
N (nodes)	
N0	No clinically abnormal peripheral lymphnodes
N1	Clinically abnormal peripheral lymphnodes
NP0	Biopsy performed, not CTCL
NP1	Biopsy performed, CTCL
LN0	Uninvolved
LN1	Reactive lymph node
LN2	Dermatopathic node, small clusters of convoluted cells (< 6 cells per cluster)
LN3*	Dermatopathic node, small clusters of convoluted cells (> 6 cells per cluster)
LN4*	Lymph node effacement
M (viscera)	
M0	No visceral metastasis
M1	Visceral metastasis
B (blood)	
B0	Atypical circulating cells not present (<5%)
B1	Atypical circulating cells present (>5%)

Abbreviation: TNMB, tumor, node, metastasis, blood.
*Pathologically involved lymph nodes.

The malignant T-cell type variably expresses CD2, CD3, CD4, CD5, CD7, and CD45RO by immunohistochemistry. The majority of cases are of the helper/inducer T-cell subset with a $CD4^+$phenotype. Rare cases of the cytotoxic/suppressor T-cell subset expressing the $CD4^-/CD8^+$ phenotype have been reported. In advanced stages, an aberrant phenotype with loss of T-cell markers is a common finding. Clonal rearrangement of the T-cell receptor (TCR) genes is demonstrated in most cases. Patients with SS and advanced MF show a helper T-cell type 1 (T_h1)/(T_h2) imbalance with a predominant type 2 immune response followed by an impaired cell-mediated immunity.[11] Peripheral eosinophilia and hypergammaglobulinemia may occur.[12]

Gene studies have shown allelic losses at 1p, 9p, 10q, and 17p with gains in chromosome 4q, 18, and 17q, microsatellite instability, and rarely mutations of *p53* in primary CTCL.[13-16] Acquired defects in apoptosis through inactivation of the *p16* gene are also reported.[17] In addition, the antiapoptotic *bcl-2* gene is overexpressed in MF and *STAT 3* (signal transducer and transcription activator) is constitutively activated in SS cells.[18]

In general, the T stage remains the best prognostic factor. However, several independent prognostic factors have been identified including the

Table 3. Stage Classification for MF/SS

Stage	T	N	NP	M
IA	1	0	0	0
IB	2	0	0	0
IIA	1/2	1	0	0
IIB	3	0/1	0	0
III	4	0/1	0	0
IVA	1-4	0/1	1	0
IVB	1-4	0/1	0/1	1

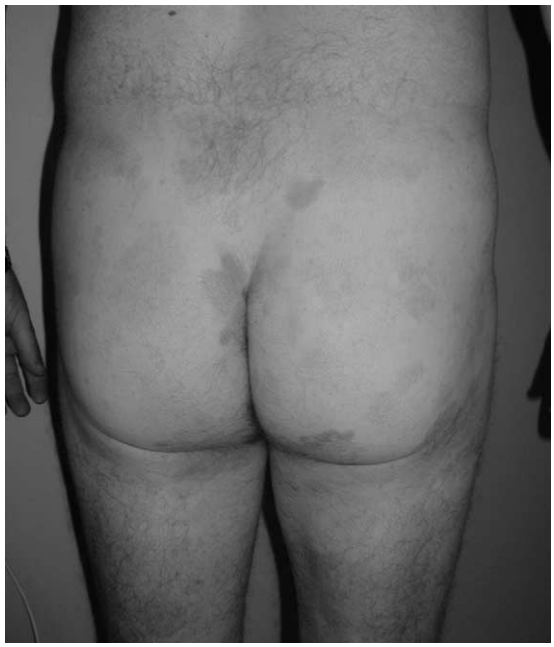

Fig 2. MF, patch stage. Multiple erythematous patches on the back and buttock area.

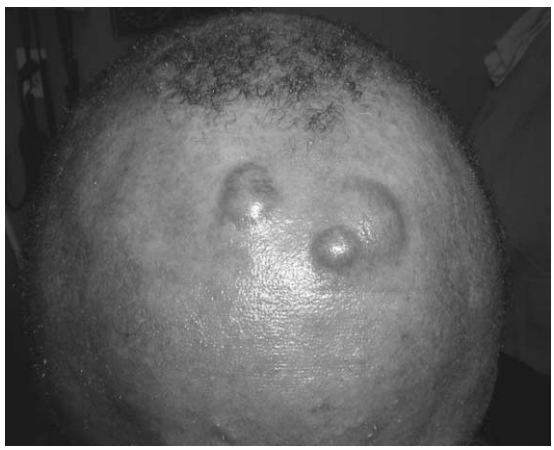

Fig 3. MF, tumor stage. Erythematous nodules on the forehead.

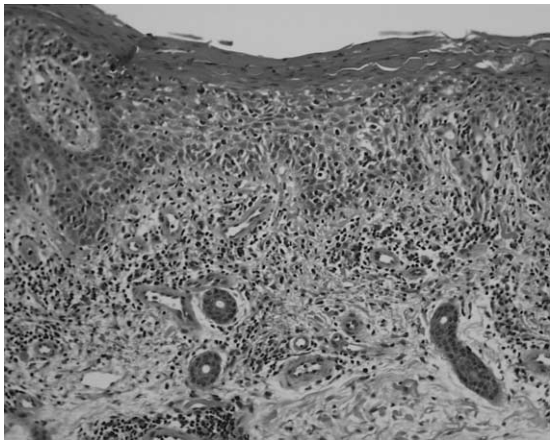

Fig 4. Histologic appearance of MF, with presence of a band-like mononuclear infiltrate and prominent epidermotropism.

presence of visceral and/or lymph node involvement, follicular mucinosis, thickness of tumor infiltrate, and an increase in lactico-dehydrogenase (LDH). More recently, other predictive factors are reported.[19-23] The presence of cytotoxic $CD8^+$ T-lymphocytes in the dermal infiltrate, as well as the density of epidermal Langerhans cells greater than 90 cells/mm^2 is associated with a better prognosis.[24,25] In contrast, large cell transformation in MF is associated with an aggressive clinical course and shortened survival (Fig 5).[26] On histology, it is defined as the presence of large cells exceeding 25% of the dermal infiltrate or nodular aggregates. Morphometric studies revealed 2 types of Sézary cells, small and large type. Patients with large Sézary-cells were found to have a worse prognosis. A high Sézary cell count, loss of T-cell markers such as CD5 and CD7, existence of a T-cell clone in the blood and chromosomal abnormalities in T cells is also independently associated with a poor outcome.[27]

CTCL VARIANTS

Lymphomatoid Papulosis

Lymphomatoid papulosis (LyP) represents a cutaneous $CD30^+$ lymphoproliferative disorder with histologic features resembling malignant lymphoma, in contrast to the benign clinical course. However, 10% to 20% of patients may develop a lymphoid malignancy.[28a] LyP is most commonly associated with MF, $CD30^+$ LTCL, and Hodgkin's disease. The clinical features consist of recurrent eruptions of self-healing, frequently ulcerating, papulonodular lesions.[28b] Three histologic types have been identified, characterized as type A, B, and C. Type A and C consist of large lymphocytes resembling Reed-Sternberg cells. Type A cells are embedded in a dense inflammatory background, whereas type C cells form large sheets imitating $CD30^+$ LTCL. Type B simulates classical MF features with epidermotropism and a dermal band-like infiltrate composed of small to medium-sized cells.[29] Clonality of TCR has been demonstrated.[30] Recently published immunohistochemical data suggest that fascin expression in LyP may become a predictive marker for tumor progression in LyP.[31] There is no curative treatment available. PUVA, methotrexate, interferon, topical or intralesional steroids, doxycyclin, and topical bexarotene are palliative, but probably do not alter the course of the disease. These agents should be used cautiously to avoid the harmful side effects in patients with an excellent prolonged survival.

CD30 Positive Large T-Cell Lymphoma

CD30+ LTCL presents clinically as solitary or localized nodules or tumors that frequently ulcerate (Fig 6). Regional lymph node involvement is seen in 25% of patients at presentation. The neoplastic cells are of the $CD4^+$ helper T-cell phenotype with CD30 expression. This tumor has an excellent prognosis as confirmed in several studies, in contrast to the transformation of MF into a

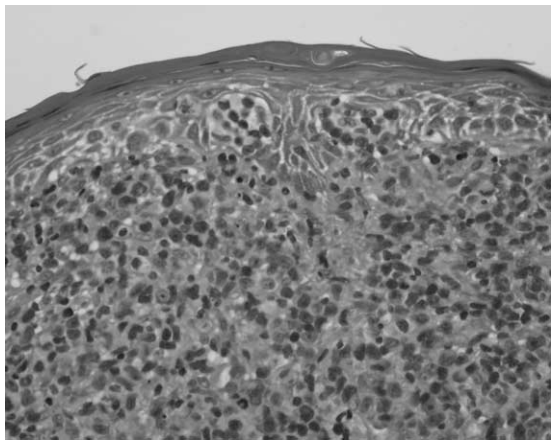

Fig 5. Histologic appearance of large cell transformation in MF, composed of large pleomorphic lymphocytes with presence of Pautrier's microabscesses.

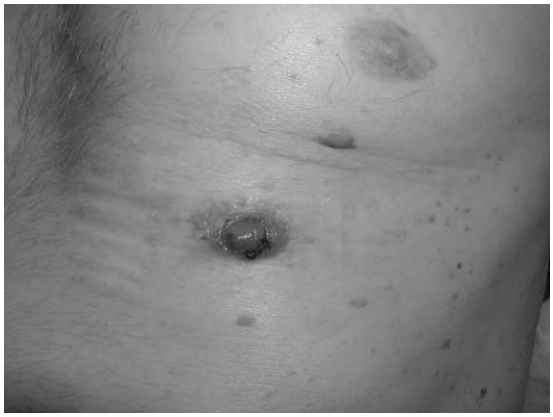

Fig 6. CD30$^+$ large T-cell lymphoma. Clinical appearance with a solitary, ulcerated tumor.

CD30$^+$ large cell variant. The characteristic histologic feature is a diffuse, nonepidermotropic infiltrate with cohesive sheets of large CD30$^+$ lymphocytes (Fig 7). In most cases, tumor cells show anaplastic features, less commonly a pleomorphic or immunoblastic appearance. However, there is no difference in the prognosis and survival rate.[32,33] T-cell clonality is demonstrated in most instances.

In contrast to their nodal counterpart, chromosomal translocation t (2;5) leading to anaplastic lymphoma kinase (ALK) expression is rarely observed. CD30+ LTCL may regress spontaneously. However, the mechanism of tumor regression remains unknown. CD30 ligand-mediated cytotoxicity may participate in the pathophysiology of clinical regression. [34,35]

Risk factors predicting tumor progression or dissemination have not been identified. However, patients with multiple lesions exhibit extracutaneous manifestations in up to 17% of cases.[20] Coexpression of CD56 and CD30 may be associated with a more aggressive behavior.[36] In cases with progression, point mutations and deletions on TGF-β receptor genes I and II have been found leading to the loss of its tumor suppressor properties.[37] Increased levels of fascin have also been correlated with disease progression.[31]

Spot radiation or surgical excision is the preferred treatment with systemic chemotherapy reserved for cases with large tumor burden and extracutaneous involvement. More recently there has been reported a therapeutic efficacy of recombinant interferon γ.[38]

CD30 Negative Large T-Cell Lymphoma

These lymphomas are aggressive neoplasms with an abysmal 15% 5-year survival rate. Patients present with solitary, localized or generalized plaques, nodules, or tumors without spontaneous regression. Microscopically, a dense, nodular or diffuse, sometimes angiocentric, and epidermotropic infiltrate characterized by pleomorphic medium or large-sized cells and immunoblastic lymphocytes is present.[39] Large cells comprise over 30% and might resemble classical MF undergoing large cell transformation. In contrast to true MF, the neoplastic T cells do not display a T_h2 cytokine profile and do not express CD30.[40] T-cell clonality is present. Multiagent systemic chemotherapy is recommended in most cases, with radiotherapy limited to localized disease.

Pleomorphic T-Cell Lymphoma With Small/Medium-sized Cells

These uncommon CTCL type appears clinically with single red-purple nodules or tumors. Histopathology shows a dermal dense, diffuse, or nodular infiltrate comprising small- and medium-sized pleomorphic cells with variable epidermotropism. Most cases express a classic T-helper cell phenotype and do not express CD30. T-cell rearrangement studies have shown clonality. The prognosis is favorable with a 5-year survival rate of 60% to 90%.[41,42] A predominance of small-sized pleomorphic cells is associated with a better prognosis whereas a CD4$^+$/CD56$^+$ phenotype with loss of pan T-cell markers

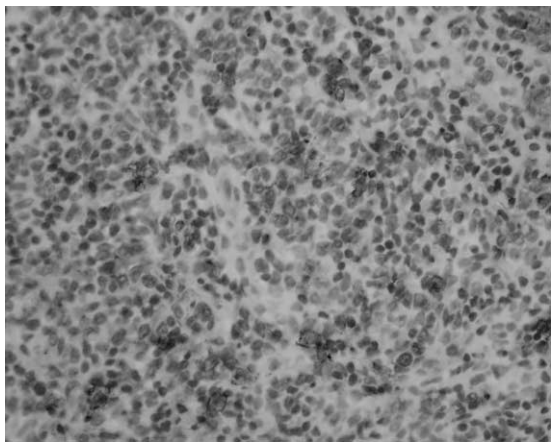

Fig 7. Histologic appearance of CD30$^+$ large T-cell lymphoma with presence of large CD30$^+$ lymphocytes.

appear to have a less favorable prognosis.[43] The optimal therapy of pleomorphic T-cell lymphoma has not been defined. Localized lesions have been treated with radiation or surgical excision. Patients with generalized skin disease or progression have been treated effective with systemic treatments including chemotherapy, retinoids, interferons, and monoclonal antibodies.

Subcutaneous Panniculitis-like T-Cell Lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is an extremely rare type of lymphoma. Approximately 100 cases are described to date. Patients, often young adults, present with subcutaneous nodules and plaques accompanied by constitutional symptoms including weight loss, fatigue, and low-grade fever. The primary subcutaneous involvement resembles panniculitis. On histology, there is a subcutaneous infiltrate including pleomorphic small- to medium-sized T cells, histiocytes, and variable component of fat necrosis, mixed inflammation, cytophagocytosis, and karyorrhexis. Two distinct patterns of TCR expression are known. The majority express α/β TCR with a $CD8^+$ phenotype, less commonly γ/δ TCR with variable $CD8^+$ phenotype which is frequently associated with systemic symptoms and hemophagocytic syndrome.[45,46] In general, the prognosis remains poor despite use of aggressive chemotherapy with an overall survival rate of less than 3 years.[47]

Granulomatous Slack Skin

This is a rare skin neoplasm characterized by large, erythematous, and indurated plaques slowly progressing into erythematous masses resembling cutis laxa-like appearance, often localized in intertriginous or flexural areas. The common histologic feature is a dense granulomatous infiltrate containing pleomorphic T cells with a varying number of histiocytes, multinucleated giant cells and elastophagocytosis. Elastic fiber destruction leads to the cutis laxa-like appearance.[48] The atypical cells usually express a $CD4^+$, and $CD8^-$ phenotype. Clonality may occur. Although patients show an indolent clinical course, 30% of patients develop other lymphomatoid malignancies. MF and Hodgkin's disease are most common associated. Treatment options include radiation, PUVA, interferons, retinoids, steroids, and surgical excision.[49] However, the assessment of therapeutic alternatives is limited because of the modest number of patients reported to date.

THERAPY

Standard treatment options are typically palliative and can be divided into skin-targeted and systemic approaches. The skin-targeted modalities includes psoralens with ultraviolet light A (PUVA), narrowband-ultraviolet light B (NB-UVB), skin electron beam radiation, as well as topical preparations of steroids, retinoids, carmustine, and nitrogen mustard. In early CTCL, the cell-mediated immune response is usually normal. Therefore, the majority of these cases can be treated successfully with topical modalities, since early aggressive therapy did not improve the prognosis of patients with CTCL. Systemic therapies are reserved for more advanced stages. Established treatment options include single-agent or multiagent chemotherapy, extracorporeal photopheresis, interferon-α or interferon-γ, monoclonal antibodies and recombinant toxins. In advanced CTCL, there is a shift from the helper T-cell type 1 (T_h1) to helper T-cell type 2 (T_h2) with up-regulation of T_h2 cytokines such as interleukin (IL)-4, IL-5, and IL-10 and downregulation of T_h1 cytokines such as IL-2 and interferon-γ leading to an impaired immune response.[50] Newer treatments such as biologic response modifiers target the reconstitution of immune function.

Photochemotherapy

PUVA is probably the preferred treatment option for early stage MF. 8-Methoxypsoralen (8-MOP) act at the nuclear level of cells, inhibiting DNA and RNA synthesis through formation of mono- or bifunctional thymine products, gene mutations, or sister chromatid exchanges.[51] In vitro studies have shown that peripheral blood mononuclear cells undergo apoptosis after exposure to PUVA.[52] 8-MOP becomes only activated when exposed to UVA light and it is usually ingested 2 hours before UVA exposure.

Initial exposure times of patients are limited to the phototype according to Fitzpatrick grading system, the ability to tan, and the patient's history of sunburns. The initial UVA dosage is approximately 0.5 J/cm^2 and will be increased per treatment as tolerated or up to the minimal erythema dose. Therapy is typically given 3 times a week

until complete remission is achieved. Additional maintenance therapy is necessary to achieve longer remission times.

Several studies confirmed high remission rates in early stages of MF. Herrmann et al [53] reported complete remissions in 65% of patients. Similar results have been reported from the Scandinavian study group.[54] Reported side effects to PUVA can be divided into more acute short-term effects including nausea from ingestion of psoralen, erythema, pruritus, and photodermatitis and long-term effects such as chronic photodamage and secondary skin malignancies.[55] Narrowband-UVB phototherapy (NB-UVB) is considered to be less carcinogenic and may be an alternative treatment option in early stage MF. However, the remission time is short.[56] A few cases have been reported showing that UVA_1 phototherapy is also effective.[57]

Radiotherapy

CTCL's are radiosensitive and radiation therapy is effective in controlling localized tumors. Total electron beam treatment (TSEBT) should be reserved for more advanced and disseminated stages, because of its potential toxicity.[58] The standard total dose is 36 Gy applied over 8 to 10 weeks. Side effects consist of erythema, edema, scaling, ulcerating, and often, irreversible loss of skin adnexa. Recently published data of therapeutic efficacy of TSEBT from Hamilton, Ontario, and Yale University showed that 60% of patients with erythrodermic mycosis fungoides achieved complete remission with a 5-year progression free duration of 26% and with more intense TSEB 74% complete remission with a 10-year progression free duration of 26%.[59] TSEB should only be used in centers with extensive experience and often requires adjuvant therapy to maintain the time of remission.

Systemic Chemotherapy

Systemic chemotherapy is defined to patients with advanced stages or with relapsed and refractory stages. Established treatment options include single-agent or multiagent chemotherapy including steroids, methotrexate, chlorambucil, doxorubicin, and etoposide.[60] Newer purine analogs such as fludarabine and 2-chloro-deoxyadenosine showed initial response rates from 28% to 66%. However, most responses were short-lived and accompanied by harmful side effects related to prolonged immunosuppression.[61,62] Temozolomide, a new oral alkylating agent, is being evaluated in a phase II trial for patients with relapsed MF and SS. Patients with MF/SS have been shown to have low levels of DNA repair enzyme O^6 alkylguanine DNA alkyltransferase (AGT) and may be particularly sensitive to this alkylator.[63,64] Pegylated Doxorubicin, empirically tested for relapsing or recalcitrant CTCL, achieved an overall response rate of 83% with tolerable side effects.[65]

BIOLOGICAL THERAPIES

Retinoids

Retinoids are vitamin A derivatives. The biological effects of retinoids are triggered through specific retinoid receptors, RAR and RXR. Well-known retinoids such as 13-cis retinoic acid (isotretinoin), etretinate, acitretin, and trans-retinoic acid exert their effects by binding to the retinoic acid receptor resulting in controlling cell growth and differentiation. All of these retinoids have been used in CTCL and several studies have evaluated their effectiveness. However, the response rates remained to be shortly.[66-68] The most common side effects include mucous membrane dryness and headache. Bexarotene, a new synthetic retinoid identified, selectively binds to the retinoid X receptor. In vitro studies have shown that stimulation of RXR induces apoptosis, which is thought to be defect in CTCL.[69] Bexarotene (300 mg/m^{2}administered daily) has been studied in several clinical trials for refractory early and advanced stage patients. The results are promising, with 54% of patients with refractory early stage and 45% of patients with refractory advanced stage, having an overall response. The median duration of response was 299 days.[70,71] Bexarotene, at recommended dosage, is associated with significant side effects, particularly hyperlipidemia and hypothyroidism. Therefore, patients should be monitored closely. It is commonly used in combination with PUVA to achieve optimal efficacy at lower dosage and increased response durability. A topical formulation as a 1% gel is also approved. It is indicated for early stage Ia and Ib of CTCL. A phase II trial demonstrated a 63% overall response rate. Side effects were restricted to the application side and were mostly mild to moderate irritation with erythema in 73% of cases.[72]

Interferons

Interferon-α (INFα) is the most effective agent in the treatment of CTCL, as verified in several studies. Monotherapies achieved significant response rates in 50% to 80% of patients.[73] T_h1 cytokines support cytotoxic T-cell mediated immunity and therefore INFα is used to boost the cell-mediated response to malignant T-lymphocytes.[74,75] It is administered sub-cutaneously, intramuscularly, or intralesionally. INFα is initiated at low doses of between 1 and 3 million international units (IU) 3 times weekly with gradually increasing as treatment is tolerated by the patient. Most common side effects are flu-like symptoms such as chills, fever, headache, myalgia, and fatigue. With less frequency, depression, cytopenia, impaired liver function test, renal and cardiac dysfunction occur.[76] IFNα is often used in combination with retinoids/rexinoids, PUVA, electron beam radiation, and extracorporeal photopheresis. The combination therapy IFNα and PUVA resulted in high response rates in more than 90% of patients and shows superiority to other combinations.[77,78] Experience with INFγ is limited. It has been shown to inhibit T_h2 cytokine production by malignant T cells. In a single trial of 16 CTCL patients with refractory disease, five patients showed partial response rates with a median duration of 10 month. The side effects are similar to those of INFα.[79]

Extracorporeal Photochemotherapy

Extracorporeal photochemotherapy or photopheresis (ECP) is a leukapheresis-based method in which 8-MOP treated blood mononuclear cells are exposed to UVA and returned to the patient. It is performed on 2 consecutive days every month. Although the mechanism of action is not completely understood, induction of apoptosis with subsequently release of tumor antigens leading to a systemic antitumor response against the malignant T-cell clone is suspected.[80,81] Few studies have reported response rates between 36% and 64% for patients with advanced disease.[82,83] Prolonged survival rates have also been reported. Ideal candidates for ECP are patients with Sézary syndrome with a short duration of disease, modest numbers of circulating atypical cells and near normal counts of circulating $CD8^+$ T- lymphocytes.[84] The results in patients with marked immunosuppression are disappointing.[85]

IL-2 Fusion Protein (Denileukin Diftitox)

Diphtherotoxin-interleukin-2 (DAB-IL-2) is a recombinant cytotoxic fusion protein that targets the IL-2 receptor on malignant and activated T-lymphocytes. It combines the receptor binding domain of IL-2 with diphtheria toxin. Once bound to the IL-2 receptor, it is internalized by endocytosis, the ADP-ribosyltransferase activity of diphtheria toxin compound is enzymatically cleaved with subsequently inhibition of protein synthesis. In phase I and II trials, 37% of patients showed an objective clinical response with a median duration of 10 month. A phase III study initiated for patients with refractory or advanced CTCL showed similar results with a 30% response rate.[86] However, predominant adverse effects including acute infusion-related hypersensitivity reaction such as fever, rash, chills, myalgias, and vascular leak syndrome have been witnessed in 74% of patients. In a subsequent study, premedication of steroids diminished the events.[87]

Recombinant IL-12

In CTCL progression marked defects in cell-mediated immunity are associated with the impaired production of T_h1 cytokines IL-2 and INFγ. In vitro studies have shown that IL-12 is a powerful inducer of INFγ production and cell-mediated cytotoxicity. Based on these findings, a phase I dose escalation trial using rIL-12 intralesionally or subcutaneously for CTCL patients was performed and showed an overall response in 56% of patients.[88] Subcutaneous application resulted in complete responses in 2 of 5 patients and partial responses in 2 of 5 patients with plaque disease and in one of 2 patients with Sézary syndrome. Recombinant IL-12 is a potent therapeutic agent. Repeated administration of rIL-12, however, results in clinical refractoriness secondary to down-regulation of the IL-12 receptor. A combination of rIL-2 and rIL-12 showed a synergistic enhancement of a cytotoxic T-cell response and upregulation of IL-12 receptors.[89] Further clinical trials are in progress to establish the effectiveness of the IL-2 plus IL-12 regimen in advanced CTCL.

Alemtuzumab (Campath-1H)

Alemtuzumab, a humanized monoclonal IgG_1 antibody, targets the CD52 antigen that is expressed on most malignant B- and T-lymphocytes, but not on hematopoietic stem cells. The mechanism of this antibody is not completely understood, but is thought to regulate antibody-dependent cellular cytotoxicity, complement-mediated cell lysis, and apoptosis. Malignant T-lymphocytes express high numbers of CD52 cell-surface marker and correlate with the clinical benefits. Alemtuzumab is currently the focus of many clinical trials in hematologic malignancies and has been used in the treatment of lymphomas and lymphoid leukemias with promising results.[90] A phase II multicenter trial with advanced and pretreated low-grade non-Hodgkin's lymphoma included 8 patients with MF/SS. Four of these patients responded and 2 achieved a complete remission.[91] A recently published study of alemtuzumab in 22 patients with advanced MF/SS recorded a clinical response in 55% of cases with 32% complete remission. The compound has an acceptable toxicity rate with mostly infusion-related events including fever, rigor, nausea, hypotension, rash, and fatigue. Cytopenias and prolonged immunosuppression require prophylactic antibiotics. The most impressive results for this agent are demonstrated in Sézary syndrome patients.[92]

CONCLUSION

At present, a stage-adapted therapy of cutaneous lymphoma is the best approach, since early aggressive therapies reveal no difference in long-term outcome. Many immunologic abnormalities in CTCL are associated with advanced disease and are caused by cytokine imbalances. The biologic response modifiers have the potential to reconstitute the immune function with a tolerable rate of adverse effects and improvement in quality of life. It is apparent that patients with advanced stages of disease are optimally treated with a combination of immune modifiers to prolong survival. Future studies will have to verify the role of this strategy. Other future directions are vaccinations that target specific TCRs or immunization via tumor-associated antigen loaded dendritic cells.

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