LYMPHOMA COALITION

Worldwide Network of Lymphoma Patient Groups

GLOBAL

SUBTYPE REPORT

Cutaneous lymphomas

The focus of this report is to review patient access to care in cutaneous lymphomas; namely therapy access, clinical trials and aspects of the patient experience.

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Overview

Cutaneous lymphomas are a group of B-cell and T-cell lymphomas which have a highly variable disease course, clinical presentation and prognosis.

In 2005, the World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) created a classification scheme specifically for cutaneous lymphomas as those used for nodal lymphomas at the time were not adequate to categorise cutaneous lymphomas.[4] Subsequent (2008, 2016) WHO classifications of lymphoid neoplasms successfully integrated key principles of the 2005 WHO-EORTC classification leading to a more general framework of understanding of the biology and clinical manifestations of lymphoid malignancies in the skin.

The journey for patients with cutaneous lymphoma is often a long and arduous path, starting with the first major hurdle, which is reaching a diagnosis. Patients have at times had to wait years before coming to a conclusive diagnosis. This is partly due to the fact that the symptoms for cutaneous lymphoma resemble that of many other skin conditions, even under the microscope. The many genetic identifiers of cutaneous lymphomas point to the need to differentiate multiple subtypes. Therefore, it is essential for diagnosis to be made with the combination of clinical, histological, immunological, and molecular data by a pathologist who has expertise in cutaneous lymphomas.

Cutaneous lymphomas are divided into cutaneous T-cell lymphomas (CTCLs) and cutaneous B-cell lymphomas (CBCLs). CTCLs are cancers of the T lymphocytes that mainly affect the skin, but can also involve the blood, lymph nodes, as well as internal organs. The two longest known subtypes of CTCL are mycosis fungoides (MF) and Sézary syndrome (SS). MF and SS are more often diagnosed in men than in women and usually are first diagnosed in people between the ages of 50 and 60 years.[8]

CBCLs represent 20-25% of all cutaneous lymphomas. Because CBCLs have an overall favourable prognosis, proper recognition is vital for appropriate therapy and to avoid over-treatment in most cases. The tumour type and the extent of cutaneous involvement are the most important prognostic factors in primary CBCL

Following diagnosis, creating a viable treatment plan is the next hurdle faced by many. The National Comprehensive Cancer Network (NCCN) provides widely accepted treatment guidelines for the treatment of cutaneous lymphoma but the challenge remains that the disease is individualistic and affects people in different ways. The symptoms are varied and the manifestations of the disease often differ from person to person.

Based on the information gathered from the Lymphoma Coalition (LC) Global Database, there is a discrepancy in the access to certain treatment protocols among LC member countries. Novel therapies for CTCL such as romidepsin and vorinostat do not have regulatory approval or funding/reimbursement in many countries. Although there are many therapies available to patients with cutaneous lymphoma, none has resulted in reliable curative outcomes and often responses are short-lived.

The LC Global Database identified 724 Phase II and Phase III trials for lymphomas, of which 63 trials include CTCL and only 11 are trials specifically for CTCL. The USA is involved in the highest number of trials (58) followed by Italy and Germany, both with 7 trials each. Access to clinical trials for those in Eastern Europe, Africa, Asia Pacific and South America is either staggeringly low or non-existent.

The LC Global Patient Survey 2016 (LC GPS 2016) was used to determine the patients experience and some of the key findings showed that the top physical conditions affecting patients were itching, skin reactions, fatigue, as well as sleeplessness and trouble concentrating. The psychosocial concerns affecting well-being included concerns about body image, depression, and fear of relapse. Cutaneous lymphomas symptoms are quite visible and sometimes challenging to cover. Even after treatment, concerns about body image, depression and loss of self-esteem are still acutely felt.

When looking at barriers to treatment, the LC 2016 GPS indicated that access to a specialty physician, personal support and access to a treatment centre were the top three concerns for those with cutaneous lymphomas.

Acknowledgements

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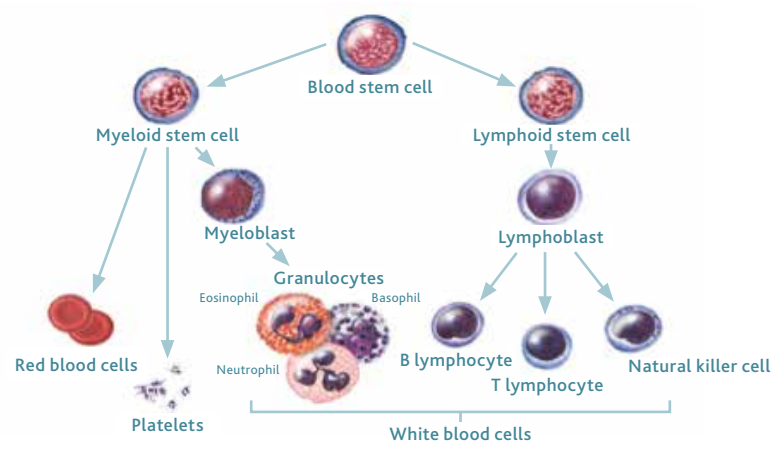
What is Cutaneous Lymphoma?

Lymphoma is the most common type of blood cancer. It originates in the lymphocytes, which are white blood cells that are a part of the body's immune system (Figure 1 shows the origin of white blood cells and red blood cells from stem cells in the bone marrow). These cells can sometimes become cancerous and start proliferating, instead of dying off. The cancerous cells can travel to other parts of the body such as the spleen, lymph nodes, bone marrow, skin and other organs. When lymphoma starts in the skin it is known as cutaneous lymphoma.

There are two main types of lymphocytes; B-cells and T-cells. Cutaneous lymphoma can originate in either the B-cell or the T-cell lymphocyte. B-cells normally help protect the body against germs (bacteria or viruses) by making proteins called antibodies.[1] These antibodies attach to the germs, marking them for destruction by other parts of the immune system.

T-cells help protect the body against viruses, fungi, and some bacteria and they orchestrate the immune response. For example, they recognize virus-infected cells and destroy them. T-cells can also release substances called cytokines that attract other types of white blood cells, which then digest the infected cells. Some types of T-cells help boost or slow the activity of other immune system cells.[1]

FIGURE 1. ORIGIN OF BLOOD CELLS[2]



Source: www.cancer.gov

The majority of lymphomas are B cell lymphomas, which account for up to **85%** of all diagnosed cases.

The opposite is true for cutaneous lymphomas; **75-80%** of all cases diagnosed as cutaneous lymphoma are T-cell lymphomas, while **20-25%** are B-cell lymphomas.[3]

In 2005, the World Health Organization–European Organization for Research and Treatment of Cancer (WHO EORTC) created a classification scheme specifically for cutaneous lymphomas as those used for nodal lymphomas at the time were not adequate to categorise cutaneous lymphomas.[4]

Subsequent (2008, 2016) WHO classifications of lymphoid neoplasms successfully integrated key principles of the 2005 WHO-EORTC classification, leading to a more general framework of understanding of the biology and clinical manifestations of lymphoid malignancies in the skin.

Studies on cutaneous T-cell lymphomas (CTCLs) show that incorrectly identifying types of CTCL or cutaneous B-cell lymphoma (CBCLs) under the microscope can lead to erroneous conclusions about the course of the disease and consequently the treatment of it. As an example, primary cutaneous large T-cell lymphomas that express the CD30+ antigen, will generally have a significantly better prognosis than systemic CD30+ large T-cell lymphomas.[5] Identification, therefore, has to be based on a combination of both clinical and histologic findings.

It is far more common however, that cutaneous lymphoma be misdiagnosed as benign skin conditions such as eczema or psoriasis. Often is it is only when treatments fail for these conditions that an alternative diagnosis is considered.

The journey for patients with cutaneous lymphoma is often a long and arduous path, starting with the first major hurdle, which is reaching a diagnosis. Patients have at times had to wait years before coming to a conclusive diagnosis of their lymphoma and subclass of cutaneous. This is partly due to the fact that the symptoms for cutaneous lymphoma resemble that of many other skin conditions, even under the microscope. It is only with further investigation by an expert in the field of cutaneous lymphoma, and often multiple biopsies reviewed by an experienced dermatopathologist, before a definitive diagnosis can be made.

With skin conditions, patients are usually referred to a dermatologist rather than an oncologist; which leads to another challenge – proper coordination of diagnosis and treatment. It is essential that the physician, whether a dermatologist or haematologist, be an expert in cutaneous lymphoma.

Ideally a patient should be seen by a multi-disciplinary team with collaboration between the dermatologist, oncologist, pathologist and radiologist.

This is only possible in some cancer care centres and providing this level of care is extremely challenging in many areas because specialists may not be available locally and patients may need to travel long distances to be seen by one.

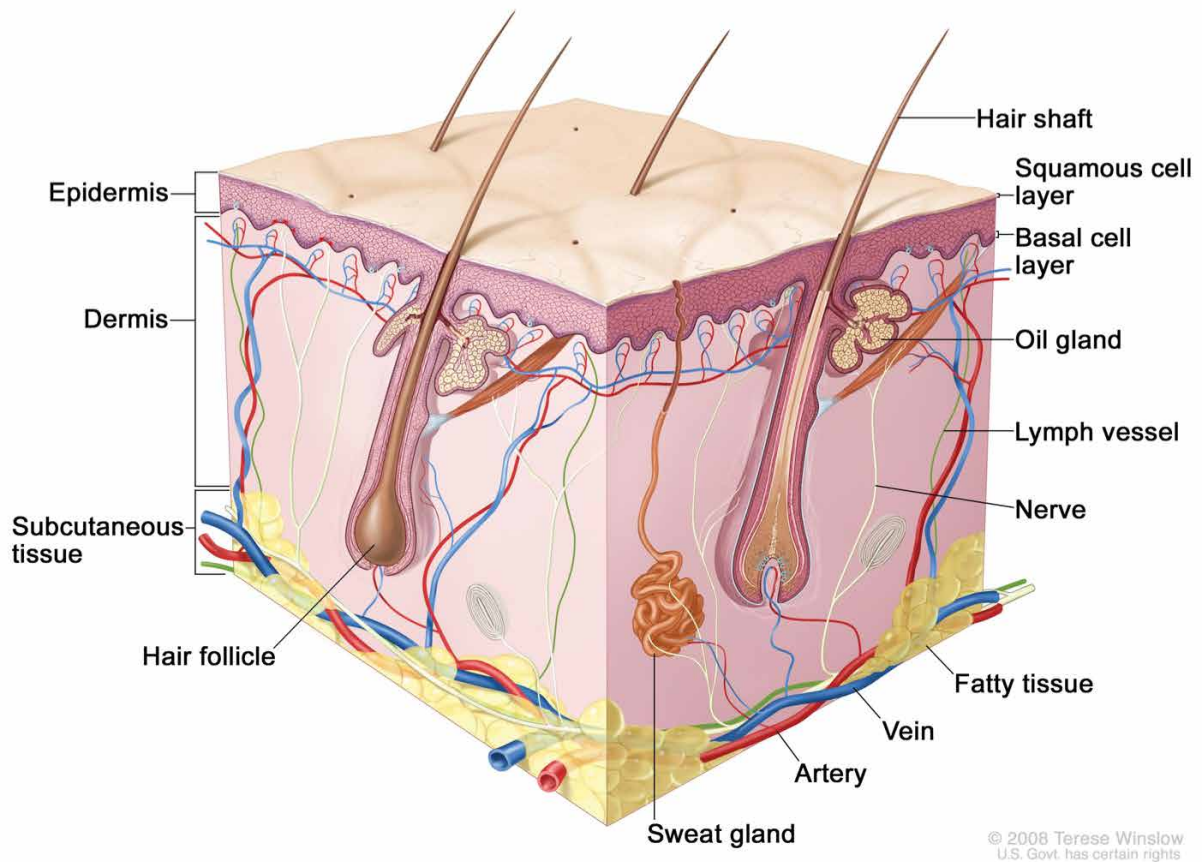
Following diagnosis, creating a viable treatment plan is the next hurdle faced by many. The NCCN provides widely accepted treatment guidelines for the treatment of cutaneous lymphoma, but the challenge remains that the disease is individualistic and affects people in different ways. The symptoms are so varied and the manifestations of the disease usually differ from person to person. For some patients ultraviolet light treatment for early stage is effective, while for others a combination of topical and systemic treatment is required and the treatment may go back and forth over time as the disease changes.

Patients who are treated and diagnosed in the early stages typically have excellent outcomes and, although treatments are not curative, symptoms can be very well controlled.

Apart from the diagnosis and treatment concerns that patients may face, there are also numerous psychosocial challenges faced by cancer patients. Many cutaneous lymphoma patients have to 'wear' their cancer, adding another dimension to the difficulties that they face.

It is important to learn more about the pathogenesis of the cancer to ensure early detection. As researchers learn more about the underlying biology and epigenetics, the hope is that curative treatments will be more widely accessible.

FIGURE 2. ANATOMY OF THE SKIN[7]



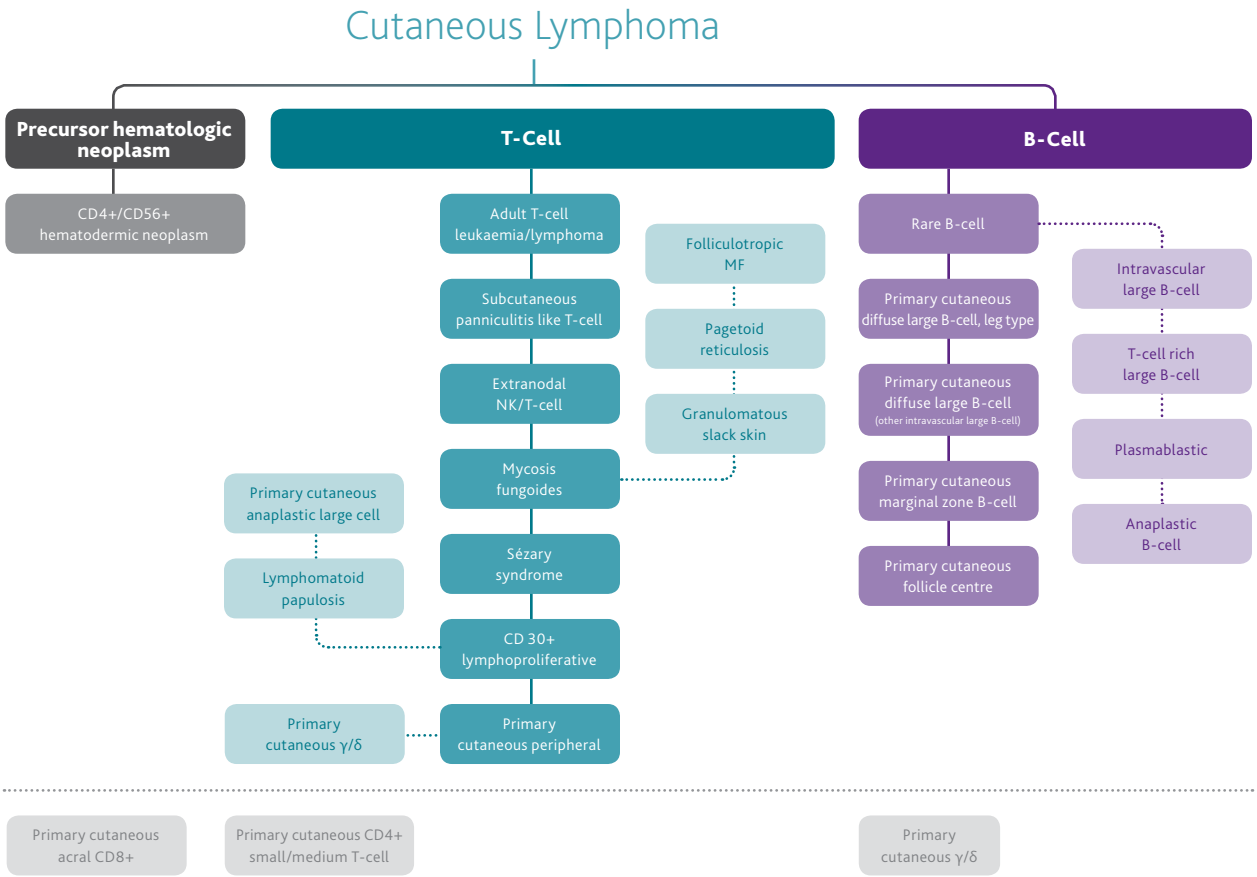
Source: www.cancer.gov

Understanding the Subclasses of Cutaneous Lymphoma

Cutaneous lymphomas are a group of B-cell and T-cell lymphomas which have a highly variable disease course, clinical presentation and prognosis.

The many genetic identifiers of cutaneous lymphomas point to the need to differentiate multiple subtypes. Therefore, it is essential for diagnosis to be made with the combination of clinical, histologic and immunologic data by a qualified dermatopathologist. Cutaneous lymphoma is divided into cutaneous T-cell lymphoma (CTCL) and cutaneous B-cell lymphoma (CBCL) with further stratification shown in Figure 3.

FIGURE 3. CLASSIFICATION OF CUTANEOUS LYMPHOMAS BASED ON WHO-EORTC[5]



Now deemed as provisional entities. Were previously included in the 2008 classification but are no longer considered to have significant malignant potential. Clinical behaviour is usually indolent and therefore terminology has been revised.

Important to distinguish from other cutaneous lymphomas that may have also been derived from γ/δ cells such as MF.

Adapted from: WHO-EORTC classification for cutaneous lymphomas

Cutaneous T-cell Lymphomas

CTCLs are cancers of the T lymphocytes that mainly affect the skin but can also involve the blood, lymph nodes as well as internal organs. The two main subtypes of CTCL are mycosis fungoides (MF) and Sézary syndrome (SS). MF and SS are more often diagnosed in men than in women and usually are first diagnosed in people between the ages of 50 and 60 years.[8] The subgroup primary cutaneous CD30+lymphoproliferative diseases encompasses a broad spectrum of CTCL diseases, representing approximately 25% of CTCLs.[1]

Mycosis Fungoides (MF)

MF is the most common type of cutaneous lymphoma accounting for almost 70% of T-cell lymphomas. It is indolent in nature and patients often deal with chronic conditions before as well as after being diagnosed. It generally affects adults over 50, although younger children have been diagnosed with MF. Most individuals with MF develop skin lesions which are pink and/or red flat, scaly patches that can be itchy. Cancerous T-cells can be found in these lesions. Diagnosis can sometimes take months or even years. A punch biopsy is recommended in order to diagnose MF.

Research suggests that certain variants of human leukocyte antigen (HLA) class II genes are associated with MF. HLA genes help the immune system distinguish the body's own proteins from proteins made by foreign invaders (such as viruses and bacteria). Certain variations of HLA genes may affect the risk of developing MF or may impact progression of the disorder.[12]

MF has many variants with three clearly defined by the WHO-EORTC: folliculotropic MF, pagetoid reticulosis and granulomatous slack skin.

There are also other rare variants of MF such as hypopigmented MF, which tends to occur in darker skinned individuals particularly of African, Indian and Latin American heritage. It presents with hypopigmented or white patches and can often be misdiagnosed as vitiligo. It is important for patients to speak to their doctor about their symptoms for an exact diagnosis of their cancer.

TABLE 1. SUBGROUPS OF MF

Subgroup of MF	Clinical features[13]
Folliculotropic MF	• Localised form of CTCL with an enlarging patch, plaque or tumour • Biopsy shows lymphomatous change around hair follicles • Skin lesions often look like bald spots (alopecia), and sometimes there is excessive production of mucus
Pagetoid reticulosis	• Localised patches or plaque with growth of neoplastic T-cells within the epidermis • Presents as a solitary psoriasis-like patch or plaque, usually on the extremities (Figure 4)
Granulomatous slack skin	• Extremely rare subtype characterised by redundant, wrinkled or inelastic skin • Occurs most commonly in the groin and underarm regions

Sézary Syndrome (SS)

SS is named after Albert Sézary, a French dermatologist born in 1880. The disease's origin is believed to be a peripheral CD4+ T-lymphocyte, although rarer CD8+/CD4- cases have been observed.[14] Sézary cells are large atypical mononuclear cells with a large cerebriform nuclei. They are found in large numbers in the peripheral blood of patients with Sézary syndrome. Flow cytometry can demonstrate CD4+CD7- and CD4+CD26- T-cells, which are characteristic of this disease.[13] Sézary syndrome commonly occurs in adults over age 60 and generally progresses rapidly; historically, affected individuals survived an average of 2 to 4 years after development of the condition, although survival has improved with newer treatments.

The cancerous T-cells can spread to other organs in the body, including the lymph nodes, liver, spleen, and bone marrow. In addition, affected individuals have an increased risk of developing another lymphoma or other types of cancer.

People with Sézary syndrome develop a red, severely itchy rash (erythroderma) that covers the majority of their body. Sézary cells are found in skin biopsies from the rash, but are not always easy to see and therefore diagnosing Sézary syndrome with a skin biopsy is challenging. Other common signs and symptoms of this condition include enlarged lymph nodes, alopecia, thickened skin on the palms of the hands and soles of the feet, abnormalities of the fingernails and toenails, and lower eyelids that turn outward.[15]

CD30+ Lymphoproliferative Disorders

CD30+ lymphoproliferative disorders represents a broad spectrum of disease within CTCL. These include CD30+ cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis, as well as borderline cases. These entities comprise approximately 25% of all CTCLs.[1] Primary cutaneous CD30+ lymphoproliferative diseases demonstrate a wide spectrum of clinical and histologic manifestations but share a common biology, which is the presence of CD30+ T-cells. Clinicians and pathologists need to be aware of the characteristic features of these entities to avoid misdiagnosis and inappropriate treatment.

Recent progress in immune and molecular biology, as well as identification of therapeutic targets, have increased our understanding of these cancers and have led to novel treatment approaches.[1]

The presentation of CD30+ lymphoproliferative diseases can be a diagnostic challenge, as CD30 expression has been observed in a variety of conditions such as arthropod bites, scabies, Langerhans cell histiocytosis, cutaneous B-cell lymphomas with immunoblastic or large-cell features, and CD30+ large-cell transformation of MF. Therefore, clinicopathologic correlation is mandatory to establish a diagnosis and to avoid inadequate or excessive therapy.[16]

TABLE 2. SUBGROUPS OF CD30+ LYMPHOPROLIFERATIVE DISORDERS

Subgroup of CD 30+ lymphoproliferative disorders	Clinical features[13]
Primary cutaneous anaplastic large cell lymphoma	• Solitary or localised nodules or tumours, often ulcerated • Regional lymph nodes may become involved in 10% of patients • Prognosis is generally favourable
Lymphomatoid papulosis (LyP)	• Lesions occur predominantly on the trunk and limbs • Lesions clear spontaneously within 3-12 weeks, and may leave behind superficial scars • Recurrences throughout the cancer duration which may be from several months to more than 40 years

Adult T-cell Leukaemia/Lymphoma

Adult T-cell leukaemia/lymphoma (ATLL), is a blood disease in which there are large numbers of circulating atypical cells. It is caused by a retrovirus infection with human T-lymphotropic virus (HTLV I). The condition can be divided into acute and chronic types. Some forms of ATLL are characterised by skin lesions similar to those found in MF and SS, enlarged lymph glands, high levels of calcium in the blood and bone lesions. Prognosis is poor for the acute type with survival ranging from a few weeks to more than a year. Chronic ATLL presents with skin lesions only and has a longer clinical course and survival, however this may transform into an acute phase that runs a more aggressive course.[13]

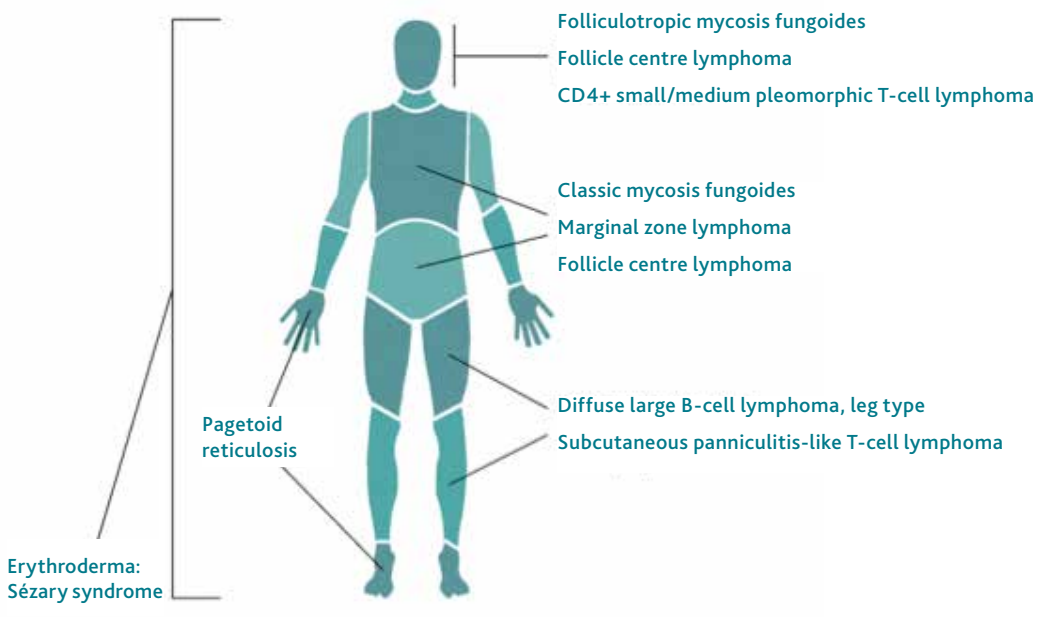
Extranodal Natural Killer T-cell Lymphoma

When extranodal natural killer T-cell lymphoma (ENKTL) initially present itself in the skin it is known as primary cutaneous ENKTL (PC-ENKTL). It is a very rare disease with a higher prevalence in Asia, Central and South America, but the real frequency is difficult to establish because of the scarcity of data. Almost all cases on PC-ENKTL present the Epstein-Barr virus, indicating the virus may be responsible for the onset of this particular lymphoma.[10]

Subcutaneous Panniculitis-like T-cell Lymphoma (SPTCL)

SPTCL is a very uncommon subtype of CTCL. The manifestations of this rare disease are atypical at onset, and may look like rheumatic or dermatologic diseases, which causes the delay of diagnosis and treatment. SPTCL may often present itself as painless, multiple subcutaneous nodules on the extremities and trunk (Figure 4). Meticulous examinations of slides are essential in a case of panniculitis as the diagnosis of SPTCL can be easily missed if this possibility is not included in the differential diagnosis of patients.[18] The cause of SPTCL is unknown, though genetic factors may play a role in its development. In order to avoid a delay in diagnosis and inappropriate treatment, in addition to a thorough physical examination, PET-CT and disease-specific pathologic, immunophenotypic, and T-cell receptor tests of the skin biopsy should be performed. The results from these special tests must be interpreted with caution as there are many overlaps between benign cells and malignant cancer cells.

FIGURE 4. DIAGNOSIS BASED ON BODY SITE[32]



The staging for CTCL is different to that of other lymphomas, particularly for MF and SS.

MF and SS are staged based on 4 factors:[20]

1. T describes how much of the skin is affected by the lymphoma and what type of lesions are present (patches, plaques, tumours).
2. N describes the extent of the lymphoma in the lymph nodes.
3. M is for the spread (metastasis) of the lymphoma to other organs.
4. B is for lymphoma cells in the blood.

Once the values for T, N, M and B are determined they are combined to determine the overall stage of the lymphoma called 'stage grouping'. The grouping is shown in Table 3.

More needs to be learned about the risk of stage progression in MF/SS and the effect of treatment on this risk, the prognostic factors beyond TNMB staging, the optimal way to describe the involvement of multiple sites, the treatment of large cell transformation, and the best time to initiate systemic therapy.

TABLE 3. STAGING OF MF AND SS[19]

Stage	
IA	Less than 10% of the skin surface is covered with patches and/or plaques
IB	10% or more of the skin surface is covered with patches and/or plaques
IIA	Any amount of the skin surface is covered with patches and/or plaques; lymph nodes are enlarged but not involved with lymphoma
IIB	One or more tumour lesions are found on the skin. Lymph nodes may be enlarged but do not contain cancerous cells
III	Erythrodermic skin, defined as a diffuse pattern of skin involvement, where greater than 80% of the body surface is involved with red patches or plaques. Lymph nodes may be enlarged but do not contain cancerous cells
IVA and IVB	Any amount of the skin surface is covered with patches, plaques or tumours. Cancer involves lymph nodes and/or blood. Cancer involves other organs in the body (stage IVB). Patients with SS have a significant level of circulating cancer cells as determined by special evaluation of the blood, either by flow cytometry or blood smear

Cutaneous B-cell Lymphomas

B-cell lymphomas account for the majority of nodal lymphomas, whereas primary cutaneous B-cell lymphomas (CBCLs) represent 20-25% of all cutaneous lymphomas. Because CBCLs have an overall favourable prognosis, proper recognition is vital for appropriate therapy and to avoid over treatment in most cases. The tumour type and the extent of cutaneous involvement are the most important prognostic factors in primary CBCL.[21, 22, 23]

The WHO/EORTC classification of CBCLs includes the following categories:[24, 1]

- Primary cutaneous marginal zone B-cell lymphoma
- Primary cutaneous follicle centre lymphoma
- Cutaneous diffuse large B-cell lymphoma, leg type and others
- Intravascular large B-cell lymphoma

Primary Cutaneous Marginal Zone B-cell Lymphoma (PC-MZL)

PC-MZL is an indolent cutaneous lymphoma, accounting for approximately 10% of all cutaneous lymphomas. Variants include immunocytoma and primary cutaneous plasmacytoma. Although it has been reported in children, it is most commonly seen in patients in their 40s.[25, 26] The prognosis of PC-MZL, has a 5-year survival rate of greater than 95%. It is most commonly located on the torso and arms (Figure 4).

Primary Cutaneous Follicle Centre Lymphoma (PC-FCL)

PC-FCL is an indolent lymphoma of follicle centre cells. The prevalence rate is approximately 12%.

Primary cutaneous FCL has an excellent prognosis, with a 5-year survival rate of greater than 90%. It recurs in up to 40% of patients.[1, 27] Extracutaneous spread occurs very rarely.[28]

Tumours are found most frequently in the scalp, neck and trunk area (Figure 4), but they are also found in other locations of the body.[27]

Primary Cutaneous Diffuse Large B-Cell Lymphoma – Leg type

PC-DLBCL is an aggressive CBCL that accounts for approximately 6% of all cutaneous lymphomas. It is associated with a relatively poor prognosis compared with other primary CBCLs, with a 5-year survival rate of 20-55%, and it tends to spread to lymph nodes and extracutaneous sites.[23,27] Two groups of primary cutaneous DLBCL have been differentiated: leg type and DLBCL, other. The leg type usually occurs on the lower legs of elderly women (Figure 4).

The precise cause of cutaneous lymphomas is still unclear. It is possible that environmental exposure or certain bacterial or viral infections are involved in the development of this disease.[33] However, the influence of genetic and environmental factors on the development of this complex cancer remains unclear.

Therapy Recommendations and Guidelines

Treatment recommendations for patients with cutaneous lymphoma are based on many factors due to the heterogeneity of the cancer as well as its variable disease course. These factors include not only age and patient's overall health, but also, more importantly, the subclass of the lymphoma. Treatment will also differ based on whether the patient is at an early stage or advanced stage of disease progression.

For the purpose of this report LC has used information from published treatment listings and guidelines which include the National Comprehensive Cancer Network (NCCN) listing, the European Society of Medical Oncology (ESMO) and the European Organisation of Research and Treatment of Cancer (EORTC). It is important to note that there is restricted high quality evidence to support the guidelines as there are few randomized trials for cutaneous lymphoma. Treatment options are outlined in Tables 4 and 5.

Cutaneous B-cell Lymphomas (CBCL)

The rarity of CBCLs and lack of comparative prospective, randomised studies limit the choice of therapy as most treatments are based on data from small retrospective studies. The European Organisation for Research and Treatment of Cancer Cutaneous Lymphoma Group (EORTC-CLG) and the International Society for Cutaneous Lymphoma (ISCL) have uniform recommendations on treating the three main types of CBCL.

The treatment recommendations in the NCCN listing and the ESMO guidelines for CBCL are shown in Table 4. Cutaneous B-cell lymphoma is commonly treated using radiation therapy (RT), rituximab and systemic chemotherapy such as RCHOP.[30] PC-DLBCL leg type is a more aggressive form of CBCL and there are no formal guidelines recorded.

There are no major differences in the guidelines for CBCL in the NCCN listing and ESMO guidelines. NCCN has additional protocols such as bexarotene, which is a retinoid, imiquimod and mechlorethamine for the first line treatment of CBCL. ESMO has interferon-alpha for relapsed patients of CBCL, which is more widely used in Europe than in North America.

TABLE 4. COMPARISON OF NCCN AND ESMO TREATMENT PROTOCOLS FOR CBCL[30,31]

NCCN		ESMO	
First Line	**Relapsed**	**First Line**	**Relapsed**
Topical corticosteroids	Topical corticosteroids	Topical corticosteroids	Topical corticosteroids
Radiation therapy	Radiation therapy	Radiation therapy	Radiation therapy
Rituximab	Rituximab	Rituximab	Rituximab
Chlorambucil ± R	Chlorambucil ± R	Chlorambucil	Chlorambucil
CVP ±Rituximab	CVP ± Rituximab		Interferon-alpha
RCHOP	RCHOP	RCHOP ± IFRT	CHOP ±R
Mechlorethamine			CVP±R
Bexarotene			
Imiquimod			

Please refer to Acronyms page

The advances in the classification, staging procedures and treatment of CBCLs have led to a major improvement in clinical care. **CBCLs for the most part have a better prognosis and positive outcomes than their nodal counterparts and it is therefore essential to get the correct diagnosis in order to avoid over treatment.**

Cutaneous T-cell Lymphomas (CTCL)

In comparing the treatment protocols recommended in the ESMO guidelines to those of the NCCN listings as shown in Table 5, there are more therapies listed by NCCN. These regimens include the newer agents such as alemtuzumab, brentuximab vedotin and bortezomib.

The overall management of CTCL is fairly complex and an individualised approach is necessary to treat it well.

Treating early stage MF with systemic agents such as gemcitabine can seriously impact the patient's immunity and overall capacity to fight the disease. The type of care and treatment needed at different stages can vary greatly, hence the recommendation by the NCCN to refer patients to a multi-disciplinary academic specialty centre. This is only possible in some cancer care centres and providing this level of care is extremely challenging in many areas because specialists may not be available locally and patients may need to travel long distances to be seen by one.

TABLE 5. COMPARISON OF NCCN AND ESMO TREATMENT PROTOCOLS FOR CTCL[30,31]

NCCN		ESMO	
First Line	**Relapsed**	**First Line**	**Relapsed**
Skin directed	*Skin directed*	*Skin directed*	*Skin directed*
Bexarotene gel	Bexarotene gel	Bexarotene gel	Bexarotene gel
Imiquimod	Extracorporeal photopheresis (ECP)	Extracorporeal photopheresis (ECP)	Extracorporeal photopheresis (ECP)
Mechlorethamine	Mechlorethamine	Mechlorethamine	Mechlorethamine
Phototherapy (UVB, NB-UVB, PUVA)	Phototherapy (UVB, NB-UVB, PUVA)	Phototherapy (UVB, NB-UVB, PUVA)	Phototherapy (UVB, NB-UVB, PUVA)
Radiation therapy	Radiation therapy	Radiation therapy	Radiation therapy
Topical corticosteroids	Topical corticosteroids	Topical corticosteroids	Topical corticosteroids
Total skin electron beam therapy (TSEBT)	Total skin electron beam therapy (TSEBT)	Total skin electron beam therapy (TSEBT)	Total skin electron beam therapy (TSEBT)
Systemic	*Systemic*		*Systemic*
Bexarotene	Alemtuzumab		Allogeneic stem cell transplant
Brentuximab Vedotin	Allogeneic stem cell transplant		Bexarotene
Gemcitabine	Bortezomib		Gemcitabine
Interferon-alpha	Brentuximab Vedotin		Liposomal doxorubicin
Liposomal doxorubicin	Chlorambucil		Methotrexate
Methotrexate	Cyclophosphamide		
Pralatrexate	Etoposide		
Romidepsin	Gemcitabine		
Vorinostat	Interferon-alpha		
	Liposomal doxorubicin		
	Methotrexate		
	Pentostatin		
	Pralatrexate		
	Romidepsin		
	Temozolomide		
	Vorinostat		

Please refer to Acronyms page

FIGURE 5. TREATMENT FOR CTCL BY STAGE

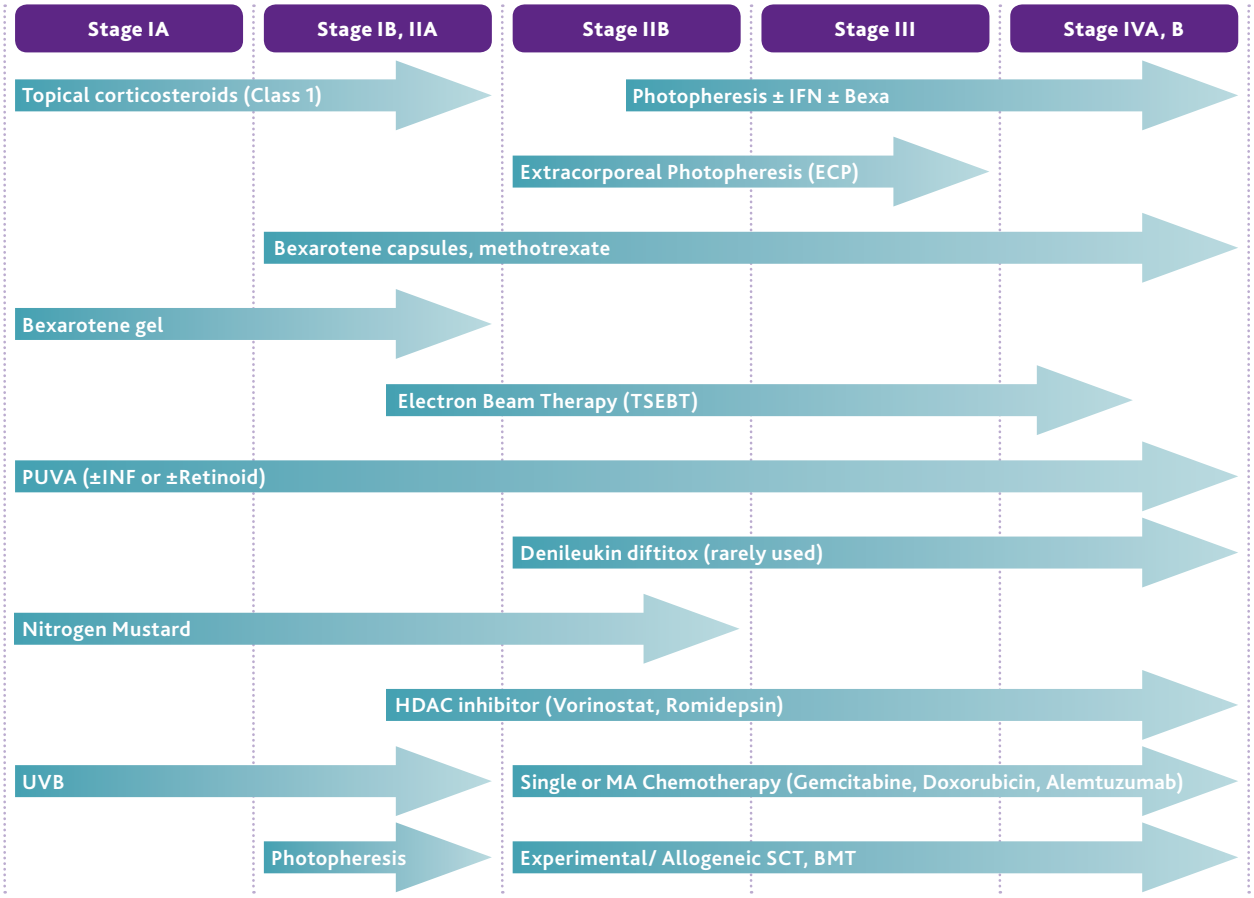


Figure 5 shows treatment options for CTCL and the different stages at which they are typically indicated.

Initial therapy usually consists of skin directed treatments. One such therapy is mechlorethamine which has been used to treat CTCL for decades. The Food and Drug Administration (FDA) and the European Commission (EC) have approved the use of mechlorethamine (chlormethine) gel for the topical treatment of MF in adults.

Radiation therapy is a mainstay of CTCL treatment, which is used either alone or in conjunction with skin-directed therapies. Although highly effective against CTCL, radiation therapy must be used judiciously because of its adverse effects.

Among the systemic agents, bexarotene, romidepsin and vorinostat (histone deacetylase [HDAC] inhibitors) are frequently used. Denileukin diftitox is currently not available.

Brentuximab vedotin and mogalumizumab are promising new drugs expected to be approved in many countries in the near future as a systemic therapy for CTCL.

It is important to note that for most treatments, direct comparisons are not available. However, recent research has led to the development of more effective biologic and targeted therapies for cutaneous lymphoma, which may lead to a more lasting remission with fewer side effects.

At this stage, despite the understanding of the biology of this cancer, there are still many questions regarding the varied disease progression. Currently the best management strategy for patients with cutaneous lymphoma is a collaborative effort among oncologists, dermatologists and other healthcare providers.

Treatment Protocol Access

Improvements in the diagnostic and prognostic guidelines for cutaneous lymphomas have assisted in the treatment of patients and if they are properly categorized in the initial phases, they can get the proper care and treatment required. This information is only useful to patients if they have access to the treatments that are needed for managing their condition.

For this report we looked at access to treatment in LC member countries for CTCL, a list of which can be found on the LC website.

Table 6 shows the specific therapies for CTCL that have regulatory approval in each member country. The therapies that are not funded/reimbursed have been highlighted. There are several LC member countries where funding/reimbursement information is unavailable, which makes it difficult to determine patient's accessibility to these treatments.

As seen in Table 6, the USA has the most therapies with regulatory approval. Access to these drugs is hard to determine as not everyone in the USA has an adequate health insurance plan.

Novel therapies for CTCL such as HDAC inhibitors, which include romidepsin and vorinostat, are not approved and/or reimbursed widely. Vorinostat has regulatory approval only in the USA, Canada, Japan and Colombia. Romidepsin in only available in Canada and the USA, where it is also reimbursed/funded.

Brentuximab vedotin is only available as a therapy for CTCL in the USA. Other novel therapies include pralatrexate, bortezomib, mogamulizumab and alemtuzumab. Alemtuzumab is reimbursed only in South Africa.

The understanding of the pathogenesis in CTCL has led to the development of targeted therapies and new drugs that have shown potentially significant activity either alone or in combination with conventional agents. However, these therapies need to be more widely accessible.

Early stage disease has shown excellent results with ECP and other skin directed therapies such as topical steroids, and mechlorethamine. Advanced stage disease requires more individualized therapies and efforts need to be made to improve quality of life.

There is no doubt that progress has been made in the treatment of CTCLs with new, innovative and promising therapies approaching. Nevertheless, there is still no curative treatment for CTCL and an urgent need exists to identify and test additional targets in well-designed clinical trials.

Dr. Pierluigi Porcu, Professor of Medical Oncology, Dermatology, and Cutaneous Biology and the Director, Division of Hematologic Malignancies and Hematopoietic Stem Cell Transplantation at Thomas Jefferson University in Philadelphia, believes more innovative thinking is needed in bridging the gaps in access to treatment and care for patients. The patients greatest needs are access to standard therapies, access to specialist care, as well as access to newly approved systemic and topical therapies. He suggested a possible solution could be to provide a centralized hub for expert assessment and treatment planning with a peripheral network where most of the care is provided, with open communication ideally through remote connectivity between healthcare professionals and also between doctors and patients. Creating a platform whereby decentralized care can be provided that is still high quality is one way of overcoming some of the barriers to treatment.

TABLE 6. THERAPY ACCESS FOR CTCL IN LC MEMBER COUNTRIES

Country	Approved therapies
Africa/ Middle East	
Algeria	Gem, MTX, RT, T-Cos, TSEBT, PUVA
South Africa	Alemtuz, Ch, CHOP, CVP, F-C, GDP, GEM-P, GCD, IGEV, INF-a, RT, T-Cos, TSEBT, PUVA
Israel	Lip-Dox, MTX, RT, SCT, T-Cos, PUVA, Mechl, Gem
Asia/ Pacific	
Australia	Gem, Lip-Dox, MTX, RT, SCT, T-Cos, TSEBT, PUVA
China	Chidamide
Japan	Lip-Dox, MTX, RT, SCT, T-Cos, TSEBT, PUVA, Vorin, Mechl, Gem, Bexa, Mogamu
New Zealand	Lip-Dox, MTX, RT, SCT, T-Cos, TSEBT, PUVA, Gem
Singapore	Bexa, Lip-Dox, MTX, RT, SCT, T-Cos, TSEBT, PUVA, Mechl, Gem
Eastern Europe	
Croatia	Bexa, Lip-Dox, MTX, RT, SCT, T-Cos, TSEBT, PUVA, Gem, Mechl
Czech Republic	Bexa, Lip-Dox, MTX, RT, SCT, T-Cos, TSEBT, PUVA, Mechl, Gem
Hungary	MTX, RT, T-Cos, TSEBT, PUVA, Gem, Bexa, Lip-Dox, SCT, Mechl
Latvia	Bexa, Lip-Dox, MTX, SCT, PUVA, Mechl, Gem, RT, T-Cos, TSEBT
Lithuania	Bexa, Lip-Dox, MTX, SCT, PUVA, Mechl, Gem, RT, T-Cos, TSEBT
Macedonia	RT, SCT, T-Cos, PUVA
Poland	Bexa, Lip-Dox, MTX, RT, T-Cos, TSEBT, PUVA, Gem, SCT, Mechl
Russian Federation	Ch, INF-a, Lip-Dox, Methoxy, MTX, RT, T-Cos, PUVA
Serbia	Lip-Dox, MTX, RT, T-Cos, PUVA, Gem, SCT, TSEBT
Slovakia	Bexa, Lip-Dox, MTX, RT, T-Cos, TSEBT, PUVA, Gem, SCT, Mechl
Slovenia	Bexa, Lip-Dox, MTX, RT, SCT, T-Cos, TSEBT, PUVA, Mechl, Gem
Turkey	MTX, T-Cos, Lip-Dox, RT, SCT, TSEBT, PUVA, Gem
Ukraine	MTX, RT, T-Cos, TSEBT, PUVA, Gem

Therapy reimbursed/funded
Therapy not reimbursed/funded

Country	Approved therapies
Latin America	
Argentina	MTX, RT, T-Cos, TSEBT, PUVA
Brazil	Lip-Dox, Mechl, MTX, RT, T-Cos, PUVA
Colombia	Lip-Dox, MTX, RT, T-Cos, PUVA, TSEBT, Vorin
Mexico	Lip_Dox, MTX, RT, T-Cos, TSEBT, PUVA, Gem, SCT
Uruguay	MTX, RT, T-Cos, SCT, TSEBT, PUVA, Gem
Venezuela	MTX, RT, T-Cos, PUVA
North America	
Canada	Bexa, C, Ch, CHOP, Gem, Lip-Dox, Mechlo, MTX, Romid, RT, SCT, T-Cos, PUVA, Vorin
United States	Alemtuz, Bexa, Bortez, BV, C, Ch, Etop, Denileukin Dif, INF-a, Lip-Dox, MTX, Pentos, Pralat, Romid, RT, SCT, T-Cos, Temoz, TSEBT, PUVA, Vorin, Mechl, Gem UVB Light
Western Europe	
Belgium	Bexa, Gem, Lip-Dox, Mechl, MTX, RT, SCT, T-Cos, TSEBT, PUVA
Bulgaria	Gem, Lip-Dox, MTX, RT, T-Cos, TSEBT, PUVA, Bexa, Mechl, SCT
Denmark	Bexa, Lip-Dox, MTX, RT, T-Cos, TSEBT, PUVA, Gem, SCT, Mechl
France	Bexa, Lip-Dox, MTX, RT, SCT, T-Cos, TSEBT, PUVA, Mechl, Gem
Germany	Bexa, Lip-Dox, MTX, RT, SCT, T-Cos, TSEBT, PUVA, Mechl, Gem
Ireland	Bexa, INF-a, Lip-Dox, MTX, RT, SCT, T-Cos, TSEBT, PUVA, Gem, Mechl
Italy	Bexa, MTX, RT, T-Cos, TSEBT, PUVA, Gem, Lip-Dox, SCT, Mechl
Netherlands	Bexa, Lip-Dox, MTX, RT, SCT, T-Cos, TSEBT, PUVA, Mechl, Gem
Portugal	Bexa, Lip-Dox, MTX, RT, SCT, T-Cos, TSEBT, PUVA, Mechl, Gem
Spain	Lip-Dox, MTX, RT, SCT, T-Cos, TSEBT, PUVA, Gem, Bexa, Mechl
Sweden	Bexa, INF-a, Lip-Dox, MTX, RT, SCT, T-Cos, TSEBT, PUVA, Mechl, Gem
Switzerland	Lip-Dox, MTX, RT, SCT, T-Cos, TSEBT, PUVA, Mechl, Bexa, Gem
United Kingdom	Bexa, MTX, RT, SCT, T-Cos, TSEBT, PUVA, Mechl, Gem, Lip-Dox

Source: Lymphoma Coalition Global Database 2017
Please refer to Acronyms page

Clinical Trials

Cutaneous lymphomas are considered a rare lymphoma accounting for approximately 4% to 5% of all lymphomas diagnosed. Although there are many therapies available to patients with cutaneous lymphoma, none have resulted in reliable curative or a long-term response. There are also toxicities associated with treatment in patients with advanced stage cutaneous lymphoma. There is, therefore, a need to investigate newer therapies that are safer and more effective.

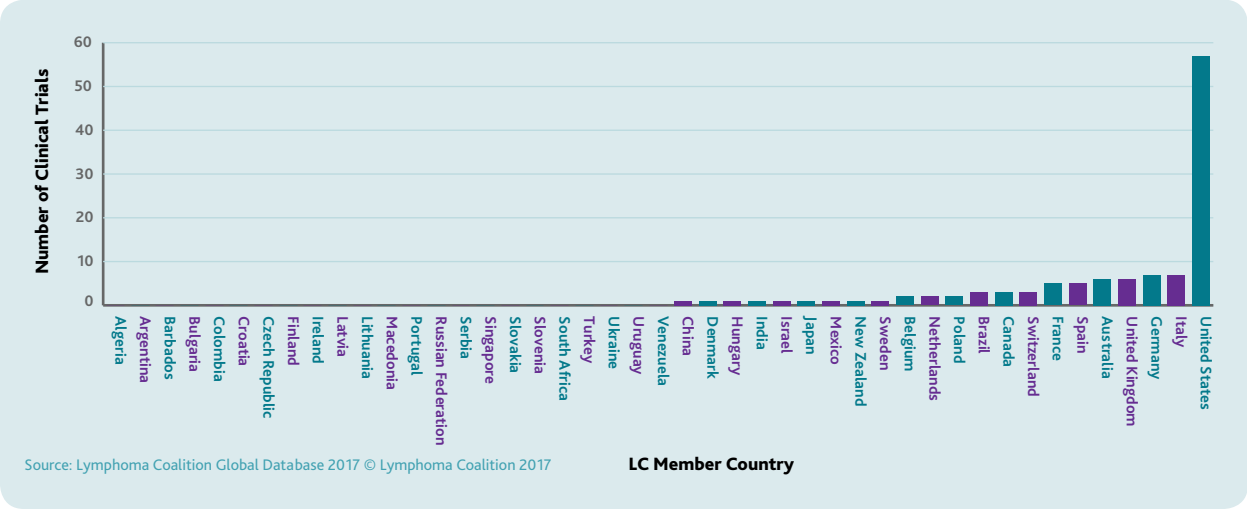
The LC Global Database identified 724 Phase II and Phase III trials for lymphomas of which 63 trials include CTCL and only 11 are trials specifically for CTCL.

As seen in Figure 6, the USA is involved in the highest number of trials (58) followed by Italy and Germany with 7 trials each. Access to clinical trials for those in Eastern Europe, Africa, Asia Pacific and South America is either staggeringly low or non-existent.

Looking at the Phase II trials, 16 are combination therapies while 29 are for novel drugs. In reviewing the distribution of clinical trials, the LC Global Database shows that a majority of trials are in the relapsed setting, while only 3 are for first line patients only. Phase II trials are looking at both first line and relapsed patients.

Patients with advanced MF and SS have a poorer prognosis leading to an interest in the development of new therapies with targeted mechanisms of action and acceptable safety profiles. It is encouraging to see that 68% of trials are for novel therapies in this area.

FIGURE 6. NUMBER OF CTCL TRIALS BY LC MEMBER COUNTRY



Source: Lymphoma Coalition Global Database 2017 © Lymphoma Coalition 2017

TABLE 7. PHASE II TRIALS

Phase II trials	Combination	Novel
Both	4	6
First Line		3
Relapse	16	29
Total	**20**	**38**

Source: Lymphoma Coalition Global Database 2017

TABLE 8. PHASE III TRIALS

Phase III trials	Novel
Both	2
Relapse	3
Total	**5**

Source: Lymphoma Coalition Global Database 2017

There are 5 Phase III trials underway, all of which are researching novel therapies, namely; brentuximab vedotin, mogamulizumab, 8-methoxypsoralen with UVA phototherapy, denileukin diftitox and SGX301 (Fluorescent Light Activated Synthetic Hypericin- FLASH).

Brentuximab vedotin is an antibody-drug conjugate (ADC) that targets CD30, which has shown promise against CTCL. The drug already has FDA approval for relapsed Hodgkin lymphoma, relapsed anaplastic large T-cell lymphoma, mycosis fungoides and lymphomatid papulosis.

Mogamulizumab has also shown great results against Sézary cells in the blood in just one or two doses.[34]

SGX301 (FLASH) is a novel, first-in-class, photodynamic therapy that combines synthetic hypericin, a photosensitiser which is applied to skin lesions and activated using fluorescent light treatment. This treatment approach avoids the risk of secondary malignancies (including melanoma) inherent with the chemotherapy and photo-dynamic therapies that rely on ultraviolet exposure.

New topical therapies are also gaining a foothold in the treatment of CTCL. The HDAC inhibitor, vorinostat, is now being tested as a cream. The oral formulation of vorinostat has multiple side effects, but these appear to be reduced with the topical formulation. Another topical drug, resiquimod, has been found to induce a local immune response that may become systemic. Researchers found that applying the agent to one lesion can clear lesions in other places on the skin. A larger trial of topical resiquimod is in the planning stages.

Other agents that are entering clinical trials for CTCL patients include phosphoinositide 3–kinase inhibitors, microRNA inhibitors, and ONC201, a compound that initiates apoptosis by engaging the cells death receptors.

There are several therapies in the pipeline, but accessibility to trials is limited for many patients. Poor accessibility can suggest the trial centre is either too far away, the eligibility criteria for the trial is prohibitive, or that there is a lack of physician and patients' awareness. There are also many instances when trials are not available in the same country as the patient. The footprint of clinical trials needs to be more widespread, particularly in underserved regions such as Latin America, Africa, Asia and Eastern Europe. Expanding into developing countries not only allows researchers access to pools of diverse patients but also provides patients with early access to innovative medication.

Patient Experience

To help us better understand the patient experience, every two years, LC engages with the global lymphoma patient community through a global survey. The results from this survey are then used to help guide LC and its member organisations with patient activities, advocacy efforts and support.

LC aims to communicate a clear picture of the patient experience and fulfil its goal of providing a voice for patients throughout their journey starting from diagnosis. The LC 2016 Global Patient Survey (GPS) is the document LC references in this section.

There were over 4,000 total respondents to the 2016 GPS, of which 145 were identified as cutaneous lymphoma respondents.

When first diagnosed with cutaneous lymphoma most patients (75%) were told their subtype. However, almost one in three did not understand their diagnosis. The number of patients who didn't understand the characteristics of their subtype was even higher at 45%. Without understanding the specifics of their diagnosis patients are unable to research the appropriate information and may miss important information relevant to their subtype.

When asked if they understood what available treatment options they had, 65% said they did and 74% felt they understood what their initial treatment would be. Yet, 30% of respondents didn't understand the side effects of treatment and 34% didn't understand how to manage the side effects. Side effects of treatment can cause stress, anxiety and if not managed correctly can sometimes be debilitating for patients.

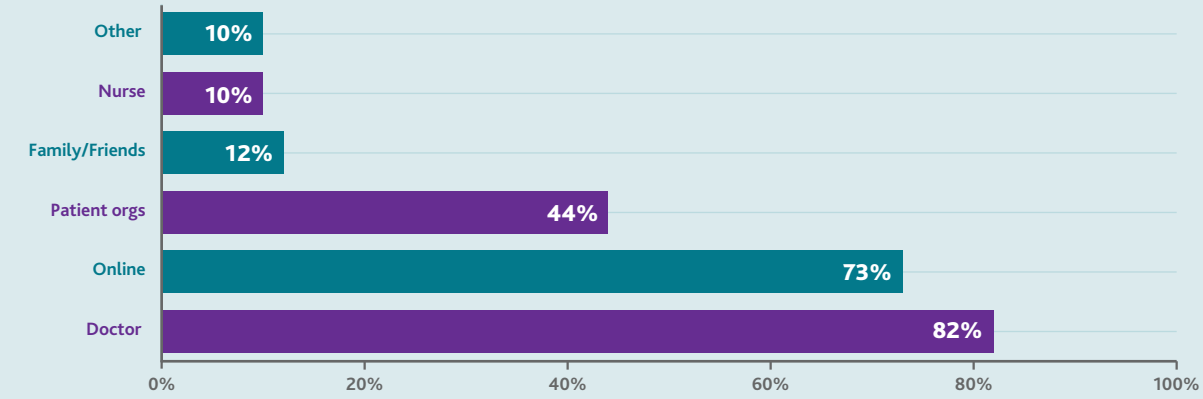
There are instances when patients don't share information with their healthcare provider about side effects for fear that they will be taken off the treatment. These fears and concerns can be alleviated with more open and active communication as well as ensuring the patient knows when to contact the doctor.

Additionally, it is important that they are made aware that reporting side effects will only help them, not hinder their care.

The LC 2016 GPS asked respondents if they communicated their emotional and physical concerns to doctors and found **59%** had while **34%** said they had not.

When asked if the doctor had helped in addressing their concerns **71%** said they had not.

FIGURE 7. PRIMARY SOURCE OF INFORMATION FOR PATIENTS, %



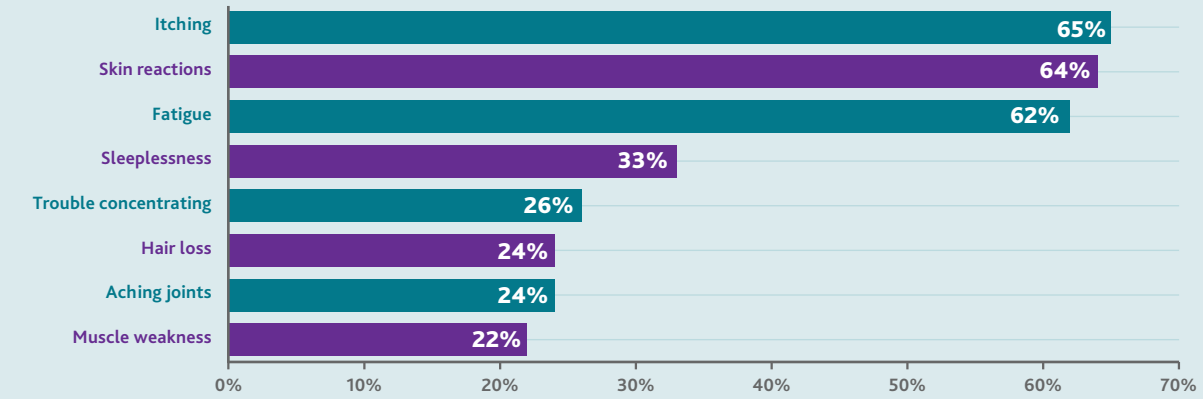
Source: LC Global Patient Survey 2016 © Lymphoma Coalition 2017

Figure 7 shows that 82% of respondents with cutaneous lymphoma got their information from doctors, but 71% indicated their doctor had not been able to help with their emotional/physical issues. It would be expected then that the internet would be the second highest source of information. Although there are many credible websites with very useful information for both patients and caregivers, the internet can also be a minefield particularly for those who don't completely understand their diagnosis or treatment protocol and don't know which are the best sites to search.

Respondents were also asked to indicate what physical conditions affected them the most. As seen in Figure 8, itching, skin reactions and fatigue are the conditions faced by patients the most, followed by sleeplessness and trouble concentrating.

With improved therapies and diagnosis, the hope is that treatment regimens can alleviate the symptoms and also reduce common side effects such as fatigue and sleeplessness, which are faced by patients across all subtypes of lymphoma.

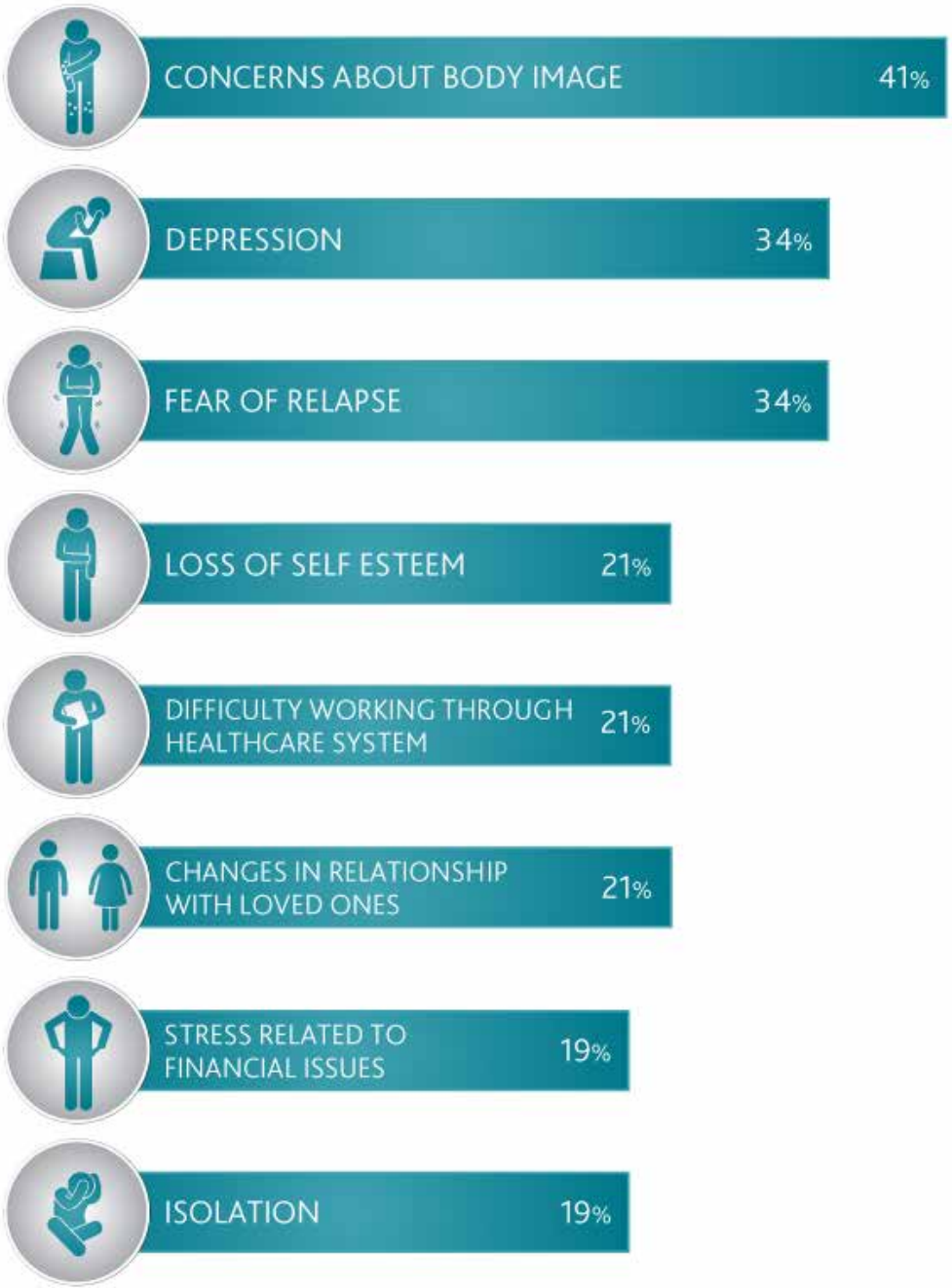
FIGURE 8. TOP PHYSICAL ISSUES FACED BY PATIENTS WITH CUTANEOUS LYMPHOMA, %



Source: LC Global Patient Survey 2016 © Lymphoma Coalition 2017

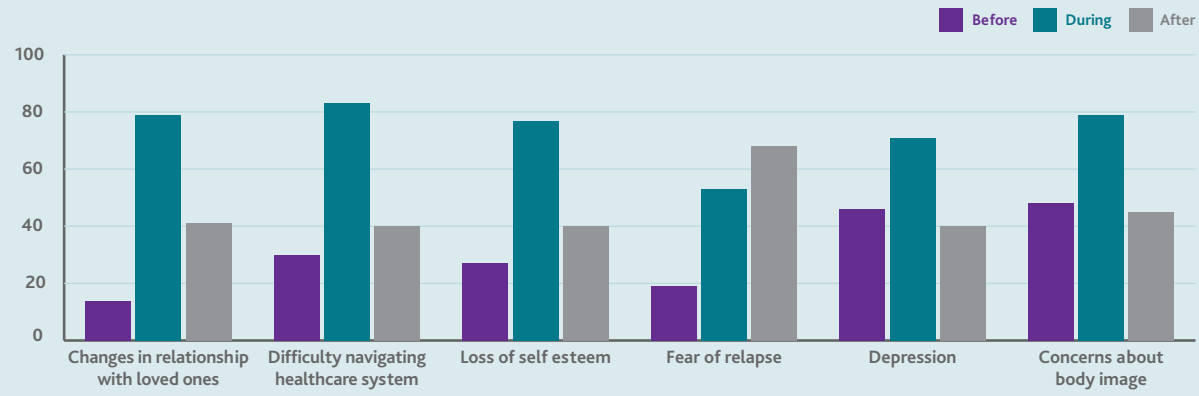
One of the challenges faced by healthcare professionals is when to treat patients, particularly those with early stage disease. Often, the decision is based on the goal of the treatment and based on the patients' needs of reducing disease burden and improving quality of life. An important factor to take into consideration is the patient's psychosocial conditions. As seen in Figure 9, one of the greatest impacts faced by patients is concern about body image, depression and fear of relapse. Cutaneous lymphomas symptoms are quite visible and sometimes challenging to cover. Even after treatment, as seen in Figure 10, concerns about body image, depression and loss of self-esteem are still acutely felt.

FIGURE 9. PSYCHOSOCIAL FACTORS IMPACTING SENSE OF WELL-BEING, %



Source: LC Global Patient Survey 2016 © Lymphoma Coalition 2017

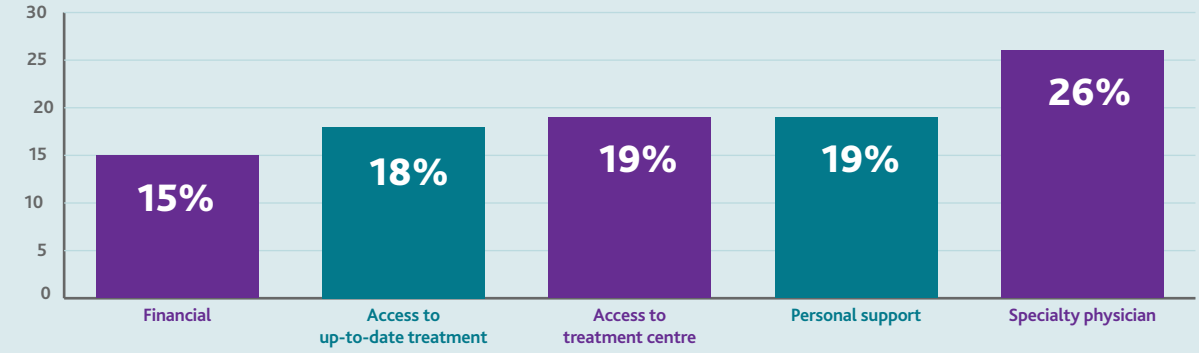
FIGURE 10. WERE YOU AFFECTED BEFORE, DURING OR AFTER TREATMENT? %



Source: LC Global Patient Survey 2016 © Lymphoma Coalition 2017

The burden of dealing with a long-term cancer can make the psychological burden of dealing with the cancer even harder. It is imperative to ensure patients have a robust support structure to rely on when their daily lives are being affected negatively.

FIGURE 11. TOP BARRIERS TO TREATMENT, %



Source: LC Global Patient Survey 2016 © Lymphoma Coalition 2017

When looking at barriers to treatment, the LC 2016 GPS indicated that access to a specialty physician, personal support and access to a treatment centre were the top three concerns for those with cutaneous lymphomas.

As mentioned earlier, access to a centre of excellence that focuses on cutaneous lymphoma is not always possible for patients. Not having access to a treatment centre or up-to-date treatment, coupled with financial difficulties, points to the struggles faced by patients who are falling through the gaps in the healthcare system.

Conclusion

It is important to remember that cutaneous lymphomas are a heterogeneous group of lymphomas that are often very difficult to diagnose. The symptoms of cutaneous lymphomas may resemble other skin conditions which adds to the challenges of correctly diagnosing the disease. Early detection and treatment requires expert oncologists, dermatologists and pathologists to work together as a team to provide the best possible care and support.

There are diverse treatment options for patients with cutaneous lymphoma, but access to treatment greatly depends on not only where you live but also the availability of a physician who specialises in cutaneous lymphomas. Not receiving expert care and exclusion from clinical trials due to lack of availability adds to the disease burden that patients face.

The hope is that ongoing clinical trials will offer patients with cutaneous lymphoma improved treatment options and better quality of life. Multi-regional trials can help patients gain access to early treatment options and give doctors the opportunity to learn about novel therapies.

The involvement of patient organisations from diagnosis through long-term care can assist patients and their families navigate the experience with the hopes of improving their quality of life.

Symptoms of cutaneous lymphomas are not only painful at times, but the effect on body image and confidence plays a huge part in the overall impact of this cancer. Patients do not always find the answers to their physical and emotional concerns on their own or through their healthcare team. This provides an opportunity for healthcare professionals and patient organisations to work together to create a robust comprehensive support structure for the patient. Acknowledging the importance of a more holistic approach to treatment that encourages psychosocial as well as clinical care can only improve the quality of care and lead to improved patient outcomes.

To ensure patients with cutaneous lymphoma receive the best possible care, it is key that the focus goes beyond the administration of therapy to include the psychological, emotional as well as physical effects associated with treatment.

Acronyms

Alemtuz	alemtuzumab
ATLL	adult T-cell leukaemia/lymphoma
Bexa	bexarotene
Bortez	bortezomib
BMT	bone marrow transplant
BV	brentuximab vedotin
C	cyclophosphamide
CBCL	cutaneous B-cell lymphoma
Ch	chlorambucil
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CT	computerised tomography
CTCL	cutaneous T-cell lymphoma
CVP	cyclophosphamide, vincristine, prednisone
Denileukin Dif	denileukin diftitox
DLBCL	diffuse large B-cell lymphoma
ECP	extracorporeal photopheresis
ENKTL	extranodal killer T-cell lymphoma
EORTC-CLG	European Organisation for Research and Treatment of Cancer Cutaneous Lymphoma Group
ESMO	European Society of Medical Oncology
Etop	etoposide
F-C	fludarabine, cyclophosphamide
FCL	follicle centre lymphoma
FLASH	fluorescent light activated synthetic hypericin
Gem	gemcitabine
GCD	gemcitabine, carboplatin, dexamethasone
GDP	gemcitabine, dexamethasone, cisplatin
ICE±R	ifosfamide, carboplatin, etoposide ± rituximab
IFRT	involved field radiation therapy
IGEV	ifosfomide, gemcitabine, vinorelbine
INF-a	interferon-alpha
ISCL	International Society for Cutaneous Lymphoma
Lip-Dox	liposomal doxorubicin
LyP	lymphomatoid papulosis
MA	multi agent
Mechl	mechlorethamine
MF	mycosis fungoides
Mogamu	mogamulizumab
MTX	methotrexate
MZL	marginal zone lymphoma
NB-UVB	narrow band UVB phototherapy
NCCN	national comprehensive cancer network
PC	primary cutaenous
Pentos	pentostatin
PET	positron emission tomography
Pralat	pralatrexate
PUVA	ultraviolet light A phototherapy
R	rituximab
RCHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
Romid	romidepsin
RT	radiation therapy
SCT	stem cell transplant
SPTCL	subcutaenous panniculitis-like T-cell lymphoma
SS	Sézary syndrome
Temoz	temozolomide
T-Cos	topical costicosteroids
TSEBT	total skin electron beam therapy
UVB	ultraviolet light B
Vorin	vorinostat
WHO -EORTC	World Health Organisation - European Organization for Research and Treatment of Cancer

References

1. https://www.cancer.org/cancer/skin-lymphoma/about/what-is-lymphoma-of-the-skin.html
2. https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=693540
3. https://www.clfoundation.org/sites/default/files/publications/2013%20Guide.pdf
4. Willemze, Rein, and Chris JLM Meijer. "EORTC classification for primary cutaneous lymphomas: the best guide to good clinical management." The American journal of dermatopathology 21.3 (1999): 265-273.
5. Willemze, Rein, et al. "WHO-EORTC classification for cutaneous lymphomas." Blood 105.10 (2005): 3768-3785.
6. Arulogun, Suzanne O., et al. "Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation." Blood 112.8 (2008): 3082-3087.
7. https://www.cancer.gov/images/cdr/live/CDR787343.jpg
8. http://www.llscanada.org/sites/default/files/file_assets/cutaneoustcelllymphoma.pdf
9. Querfeld, Christiane, et al. "Primary cutaneous CD30+ lymphoproliferative disorders: new insights into biology and therapy." Oncology (Williston Park, NY) 21.6 (2007): 689-96.
10. Hamada T, Nakamura S, Ko YH, Yoshino T, Ohshima K, Matsuzawa T, et al. "Epstein-Barr virus-associated T/natural killer-cell lymphomas in the elderly: the first consensus meeting in Kofu 2013." J Dermatol. 2014; 41:40–42. [PubMed]
11. https://www.mdanderson.org/publications/oncolog/february-2016/overcoming-challenges-in-cutaneous-t-cell-lymphomas-.html.html
12. https://ghr.nlm.nih.gov/condition/mycosis-fungoides
13. https://www.dermnetnz.org/topics/cutaneous-t-cell-lymphoma
14. Cuneo, A; Castoldi, GL, "Mycosis fungoides/Sezary's syndrome", Atlas Genet Cytogenet Oncol Haematol. 2005; 9(3):242-243.
15. https://ghr.nlm.nih.gov/condition/sezary-syndrome
16. http://www.physicianspractice.com/leukemia-lymphoma/primary-cutaneous-cd30-lymphoproliferative-disorders-new-insights-biology-and-therapy
17. http://www.cancernetwork.com/leukemia-lymphoma/primary-cutaneous-cd30-lymphoproliferative-disorders-new-insights-biology-and-therapy/page/0/3
18. Francis, Abel, et al. "Subcutaneous panniculitis-like T-cell lymphoma." Indian journal of dermatology 55.3 (2010): 290.
19. https://www.cancer.gov/types/lymphoma/patient/mycosis-fungoides-treatment-pdq#section/_26
20. https://www.cancer.org/cancer/skin-lymphoma/detection-diagnosis-staging/staging.html
21. Grange F, Beylot-Barry M, Courville P, Maubec E, Bagot M, Vergier B, et al. "Primary cutaneous diffuse large B-cell lymphoma, leg type: clinicopathologic features and prognostic analysis in 60 cases." Arch Dermatol. 2007 Sep. 143(9):1144-50.
22. Kodama K, Massone C, Chott A, Metze D, Kerl H, Cerroni L. "Primary cutaneous large B-cell lymphomas: clinicopathologic features, classification, and prognostic factors in a large series of patients." Blood. 2005 Oct 1. 106(7):2491-7. [Medline].
23. Paulli M, Lucioni M, Maffi A, Croci GA, Nicola M, Berti E. "Primary cutaneous diffuse large B-cell lymphoma (PCDLBCL), leg-type and other: an update on morphology and treatment." G Ital Dermatol Venereol. 2012 Dec. 147(6):589-602. [Medline].
24. Burg G, Kaudewitz P, Klepzig K, Przybilla B, Braun-Falco O. "Cutaneous B-cell lymphoma." Dermatol Clin. 1985 Oct. 3(4):689-704. [Medline].
25. Kempf W, Kazakov DV, Buechner SA, et al. "Primary cutaneous marginal zone lymphoma in children: a report of 3 cases and review of the literature." Am J Dermatopathol. 2014 Aug. 36(8):661-6. [Medline].
26. Amitay-Laish I, Tavallaee M, Kim J, Hoppe RT, Million L, Feinmesser M, et al. "Paediatric primary cutaneous marginal zone B-cell lymphoma: Does it differ from the adult counterpart?" Br J Dermatol. 2016 Aug 8. [Medline].
27. http://emedicine.medscape.com/article/1099540-overview#a7
28. Senff NJ, Hoefnagel JJ, Jansen PM, Vermeer MH, van Baarlen J, Blokx WA, et al. "Reclassification of 300 primary cutaneous B-Cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers." J Clin Oncol. 2007 Apr 20. 25(12):1581-7. [Medline].
29. Cetin B, Ozet A, Orhan B, Tecimer T. "A Case of Cutaneous Diffuse Large B-cell Lymphoma." Turk J Haematol. 2014 Jun. 31(2):207-8. [Medline]. [Full Text].
30. Ralfkiaer, E., et al. "Primary cutaneous CD30 T-cell lymphoproliferative disorders." Tumours of the Hematopoietic and Lymphoid Tissues (ed 4). Lyon, France, International Agency for Research on Cancer (2008): 300-301.
31. Willemze, R., et al. "Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up." Annals of oncology24.suppl_6 (2013): vi149-vi154.
32. Subtil, Antonio. "A General Approach to the Diagnosis of Cutaneous Lymphomas and Pseudolymphomas." Surgical pathology clinics 7.2 (2014): 135-142.
33. https://rarediseases.org/rare-diseases/cutaneous-t-cell-lymphomas
34. https://www.mdanderson.org/publications/oncolog/february-2016/overcoming-challenges-in-cutaneous-t-cell-lymphomas-.html

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