Cancer Association of South Africa (CANSA)

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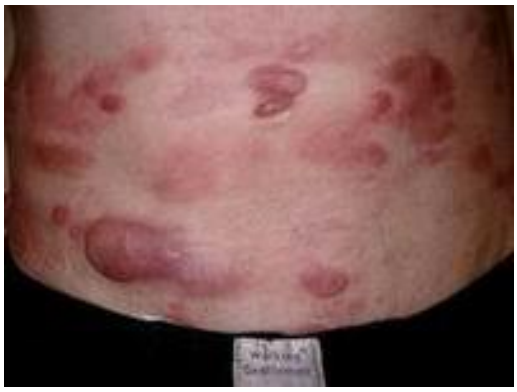
Fact Sheet
on
Mycosis Fungoides

Introduction

Mycosis fungoides, also known as Alibert-Bazin syndrome or granuloma fungoides, is the most common form of cutaneous T-cell lymphoma. It generally affects the skin, but may progress internally over time. Symptoms include rash, tumours, skin lesions, and itchy skin. While the cause remains unclear, most cases are not genetic or hereditary. It occurs mostly in people over 20 years of age, and it is more common in men than women.



[Picture Credit: Mycosis Fungoides]

Mycosis Fungoides (MF)

Mycosis Fungoides is a type of T-cell Lymphoma. Lymphoma is the most common type of blood cancer. The two main forms of lymphoma are Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL). Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. Cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a mass called a tumour. The body has two main types of lymphocytes that can develop into lymphomas: B-lymphocytes (B-cells) and T-lymphocytes (T-cells).

T-cell lymphomas account for approximately 15 percent of all NHLs. There are many different forms of T-cell lymphomas, some of which are extremely rare. Most T-cell lymphomas can be classified into two broad categories: aggressive (fast-growing) or indolent (slow-growing). One of the most common forms of T-cell lymphoma is cutaneous T-cell lymphoma (CTCL), a general term for T-cell lymphomas that involve the skin. CTCL also can involve the blood, the lymph nodes, and other internal organs. Symptoms can include dry skin, itching (which can be severe), a red rash, and enlarged lymph nodes. The disease affects men more often than women and usually occurs in men in their 50s and 60s – usually after the age of 20 although children have been diagnosed with the condition.

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Early in the course of disease, skin lesions may be non-specific, so confusion with benign (non-cancerous) conditions is common. Over time, Mycosis Fungoides becomes more aggressive, and in about 20 per cent of patients the disease will undergo a transformation to highly malignant lymphoma with widespread dissemination into various organs of the body. Late-stage disease is associated with the decline of the immune system. Death often results from systemic infection, especially with *Staphylococcus aureus* or *Pseudomonas aeruginosa*, and other organisms.

Vaidya, T. & Badri, T. 2021.
"Primary cutaneous lymphomas are the second most common extranodal non-Hodgkin Lymphomas. They may be of either T cell, B cell, or NK cell origin. Cutaneous T Cell lymphomas (CTCL) comprise a group of heterogeneous lymphomas which clinically differ from systemic lymphomas, even though they might show similar histology. Mycosis fungoides is the most common type of CTCL. It is a cutaneous lymphoma that originates in the peripheral epidermotropic T-cells, specifically the memory T-cells (CD45RO+), which express the T-cell receptor (TCR) and CD4+ immunophenotype."

Signs and Symptoms of Mycosis Fungoides (MF)
Mycosis fungoides is the most common form of cutaneous T-cell lymphoma (CTCL). It does not look the same for all patients. This form of CTCL may present itself as patches, plaques or tumours.

Mycosis fungoides - typically presents with flat, red, scaly patches that are often mistaken for eczema, psoriasis or non-specific dermatitis. Plaques are thicker, raised lesions. Tumours are raised bumps, which may or may not ulcerate (break down). A common characteristic is itching, although some patients do not experience itching. It is possible to have one or all three types of presentations.

Sezary syndrome - is another common form of CTCL, and is considered an advanced, variant of mycosis fungoides, which distinguishes itself by the presence of malignant lymphocytes in the blood.

Incidence of Mycosis Fungoides (MF) in South Africa
The National Cancer Registry (2017) does not provide any information on the incidence of Mycosis Fungoides.

According to the National Cancer Registry (2017) the following number of Non-Hodgkin's Lymphoma cases were histologically diagnosed in South Africa during 2017:

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	1 381	1:158	3,45%
Asian males	35	1:222	3,60%
Black males	804	1:223	6,13%
Coloured males	130	1:162	2,77%
White males	412	1:85	1,94%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	1 129	1:238	2,71%
Asian females	33	1:274	2,56%
Black females	658	1:343	3,51%
Coloured females	110	1:194	2,42%
White females	328	1:120	1,94%

Geller, S., Lebowitz, E., Pulitzer, M. & Myskowski, P.L. 2019.
"Incidence rates of cutaneous T-cell lymphomas (CTCL) and mycosis fungoides (MF) are higher among African American (AA) than white individuals in the United States of America. Population-based registries and single center retrospective studies have shown that AAs present with earlier onset and more advanced disease in comparison to white patients."

Diagnosis of Mycosis Fungoides (MF)
Mycosis fungoides (MF), the most common cutaneous T-cell lymphoma, is a low-grade cutaneous lymphoma characterised by skin-homing CD4+ T cells. It is notable for highly symptomatic progressive skin lesions, including patches, plaques, tumours, and erytheroderma, and has a poorer prognosis at later stages. Diagnosis remains difficult owing to MF's nonspecific skin presentation and identification of the optimal treatment strategy is challenging given the paucity of controlled trials and numerous and emerging treatment options (Galper, *et al*.).

In most cases of mycosis fungoides, the diagnosis is reached owing to its clinical features, disease history, and histomorphologic and cytomorphologic findings. An additional diagnostic criterion to distinguish CTCL from inflammatory skin conditions is demonstration of a dominant T-cell clone in skin biopsy specimens by a molecular assay (i.e., Southern blot, polymerase chain reaction [PCR]). Genetic testing may also be considered.

The following laboratory tests may be included in the diagnostic workup:
- Complete blood count with differential; review the buffy coat smear for Sézary cells
- Liver function tests: Look for liver-associated enzyme abnormalities
- Uric acid and lactate dehydrogenase levels: These are markers of bulky and/or biologically aggressive disease
- Flow cytometric study of the blood (include available T-cell–related antibodies): To detect a circulating malignant clone and to assess immunocompetence by quantifying the level of CD8-expressing lymphocytes
- Human immunodeficiency virus (HIV) and human T-lymphotropic virus type 1 (HTLV-I) testing
- Imaging studies
  - Chest radiography: To determine whether there is lung involvement
  - Abdominal/pelvic computed tomography (CT) scanning: In patients with advanced mycosis fungoides (stage IIB to IVB) or those with clinically suspected visceral disease
  - Positron emission tomography (PET) scanning: To determine visceral involvement

Staging of Mycosis Fungoides (MF)
Staging describes the severity of a person's cancer based on the size and/or extent (reach) of the original (primary) tumour and whether or not cancer has spread in the body. Staging helps the doctor plan the appropriate treatment.

Treatment of Mycosis Fungoides (MF)
Although one may be managed by a general dermatologist, MF is such a rare disease that treatment by a team of specialists is more appropriate.
The treatment team ideally should consist of physicians from different medical specialties:

- dermatologist who specialises in lymphoma
- medical oncologist
- radiation oncologist
- dermatopathologist

The simplest way to think about the multiple treatments available for MF is by dividing them into two categories: skin-directed therapies versus systemic therapies.

Skin-directed therapies are aimed at the skin primarily. The major treatments in this category include topical chemotherapy agents (nitrogen mustard or Mustargen), topical corticosteroids, topical retinoids (Targretin gel), phototherapy (PUVA, UVB), and electron beam radiation.

Systemic therapies are administered by mouth or injection and are aimed at treating the skin and/or internal organs affected or at risk. These include chemotherapy agents and biologic response modifiers (oral retinoids, interferons, fusion proteins, or extracorporal photopheresis).

Commonly, multiple treatments may be used together, which is called Combined Modality Therapy (CMT).

For each treatment option, the following paragraphs include information on treatment indications, practical use of the therapy, and potential side effects.

Whole Body Radiation and Local Radiation - mycosis fungoides is very sensitive to radiation.

Johnson, W.T., Mukherji, R., Kartan, S., Nikbakht, N., Porcu, P. & Alpdogan, O. 2018.
"Mycosis fungoides and Sézary syndrome encompass over 70% of all cases of cutaneous T-cell lymphoma (CTCL). While early stage disease has excellent long-term survival rates, advanced stage disease (IIB-IV) carries a poor prognosis with a median 5-year overall survival rate of approximately 50%. Early stage and advanced stage disease have different treatment algorithms with systemic therapy being indicated upfront in the later. The role of allogeneic hematopoietic stem cell transplant (HSCT) has gained considerable interest in recent years as a treatment option for CTCL given the increasingly promising long-term outcomes in an otherwise incurable disease."

Oral retinoids - retinoids are a class of drugs that are derivatives of vitamin A. These medications are effective in MF because they can change the growth and maturation pattern of MF cells.

Systemic chemotherapy agents - systemic chemotherapy agents are usually reserved for MF that have failed skin-directed or systemic biologic therapies or have disease that extended to lymph nodes or other internal organs.

Stem Cell Transplant

Foss, F.M. & Girardi, M. 2017.

"Mycosis fungoides and the Sezary syndrome (SS) are rare lymphomas of $CD4^+$ helper T cells. There is stagewise progression from patch/plaques to thicker tumor lesions/diffuse erythroderma. Blood involvement is a characteristic of SS. Outcomes are related to the extent of skin, blood, lymph node, and visceral organ involvement. Patients with limited patch and plaque disease are treated with skin-directed therapies. More advanced/refractory disease is treated with skin-directed therapies and oral or systemic immunomodulatory agents. Single-agent chemotherapies are used against tumors, refractory plaques, and lymph node and visceral involvement. Allogeneic stem cell transplantation is a potentially curative strategy for advanced/resistant disease."

Larocca, C. & Kupper, T. 2019.

"Cutaneous T-cell lymphomas are a heterogeneous collection of non-Hodgkin lymphomas that arise from skin-tropic memory T lymphocytes. Among them, mycosis fungoides (MF) and Sézary syndrome (SS) are the most common malignancies. Diagnosis requires the combination of clinical, pathologic, and molecular features. Significant advances have been made in understanding the genetic and epigenetic aberrations in SS and to some extent in MF. Several prognostic factors have been identified. The goal of treatment is to minimize morbidity and limit disease progression. However, hematopoietic stem cell transplantation, considered for patients with advanced stages, is the only therapy with curative intent."

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

Valipour, A., Jäger, M., Wu, P., Schmitt, J., Bunch, C. & Weberschock, T. 2020.

Background: Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma, a malignant, chronic disease initially affecting the skin. Several therapies are available, which may induce clinical remission for a time. This is an update of a Cochrane Review first published in 2012: we wanted to assess new trials, some of which investigated new interventions.

Objectives: To assess the effects of interventions for MF in all stages of the disease.

Search methods: We updated our searches of the following databases to May 2019: the Cochrane Skin Specialised Register, CENTRAL, MEDLINE, Embase, and LILACS. We searched 2 trials registries for additional references. For adverse event outcomes, we undertook separate searches in MEDLINE in April, July and November 2017.

Selection criteria: Randomised controlled trials (RCTs) of local or systemic interventions for MF in adults with any stage of the disease compared with either another local or systemic intervention or with placebo.

Data collection and analysis: We used standard methodological procedures expected by Cochrane. The primary outcomes were improvement in health-related quality of life as defined by participants, and common adverse effects of the treatments. Key secondary outcomes were complete response (CR), defined as complete disappearance of all clinical evidence of disease, and objective response rate (ORR), defined as proportion of patients with a partial or complete response. We used GRADE to assess the certainty of evidence and considered comparisons of psoralen plus ultraviolet A (PUVA) light treatment as most important because this is first-line treatment for MF in most guidelines.

Main results: This review includes 20 RCTs (1369 participants) covering a wide range of interventions. The following were assessed as either treatments or comparators: imiquimod, peldesine, hypericin, mechlorethamine, nitrogen mustard and intralesional injections of interferon-α (IFN-α) (topical applications); PUVA, extracorporeal photopheresis (ECP: photochemotherapy), and visible light (light applications); acitretin, bexarotene, lenalidomide, methotrexate and vorinostat (oral agents); brentuximab vedotin; denileukin diftitox; mogamulizumab; chemotherapy with cyclophosphamide, doxorubicin, etoposide, and vincristine; a combination of chemotherapy with electron beam radiation; subcutaneous injection of IFN-α; and intramuscular injections of active transfer factor (parenteral systemics). Thirteen trials used an active comparator, five were placebo-controlled, and two compared an active operator to observation only. In 14 trials, participants had MF in clinical stages IA to IIB. All participants were treated in secondary and tertiary care settings, mainly in Europe, North America or Australia. Trials recruited both men and women, with more male participants overall. Trial duration varied from four weeks to 12 months, with one longer-term study lasting more than six years. We judged 16 trials as at high risk of bias in at least one domain, most commonly performance bias (blinding of participants and investigators), attrition bias and reporting bias. None of our key comparisons measured quality of life, and the two studies that did presented no usable data. Eighteen studies reported common adverse effects of the treatments. Adverse effects ranged from mild symptoms to lethal complications depending upon the treatment type. More aggressive treatments like systemic chemotherapy generally resulted in more severe adverse effects. In the included studies, CR rates ranged from 0% to 83% (median 31%), and ORR ranged from 0% to 88% (median 47%). Five trials assessed PUVA treatment, alone or combined, summarised below. There may be little to no difference between intralesional IFN-α and PUVA compared with PUVA alone for 24 to 52 weeks in CR (risk ratio (RR) 1.07, 95% confidence interval (CI) 0.87 to 1.31; 2 trials; 122 participants; low-certainty evidence). Common adverse events and ORR were not measured. One small cross-over trial found once-monthly ECP for six months may be less effective than twice-weekly PUVA for three months, reporting CR in two of eight participants and ORR in six of eight participants after PUVA, compared with no CR or ORR after ECP (very low-certainty evidence). Some participants reported mild nausea after PUVA but no numerical data were given. One participant in the ECP group withdrew due to hypotension. However, we are unsure of the results

due to very low-certainty evidence. One trial comparing bexarotene plus PUVA versus PUVA alone for up to 16 weeks reported one case of photosensitivity in the bexarotene plus PUVA group compared to none in the PUVA-alone group (87 participants; low-certainty evidence). There may be little to no difference between bexarotene plus PUVA and PUVA alone in CR (RR 1.41, 95% CI 0.71 to 2.80) and ORR (RR 0.94, 95% CI 0.61 to 1.44) (93 participants; low-certainty evidence). One trial comparing subcutaneous IFN-α injections combined with either acitretin or PUVA for up to 48 weeks or until CR indicated there may be little to no difference in the common IFN-α adverse effect of flu-like symptoms (RR 1.32, 95% CI 0.92 to 1.88; 82 participants). There may be lower CR with IFN-α and acitretin compared with IFN-α and PUVA (RR 0.54, 95% CI 0.35 to 0.84; 82 participants) (both outcomes: low-certainty evidence). This trial did not measure ORR. One trial comparing PUVA maintenance treatment to no maintenance treatment, in participants who had already had CR, did report common adverse effects. However, the distribution was not evaluable. CR and OR were not assessable. The range of treatment options meant that rare adverse effects consequently occurred in a variety of organs.

Authors' conclusions: There is a lack of high-certainty evidence to support decision making in the treatment of MF. Because of substantial heterogeneity in design, missing data, small sample sizes, and low methodological quality, the comparative safety and efficacy of these interventions cannot be reliably established on the basis of the included RCTs. PUVA is commonly recommended as first-line treatment for MF, and we did not find evidence to challenge this recommendation. There was an absence of evidence to support the use of intralesional IFN-α or bexarotene in people receiving PUVA and an absence of evidence to support the use of acitretin or ECP for treating MF. Future trials should compare the safety and efficacy of treatments to PUVA, as the current standard of care, and should measure quality of life and common adverse effects.

Trial

Registration: ClinicalTrials.gov NCT00030589 NCT00050999 NCT01578499 NCT00630903 NCT00091208 NCT01386398 NCT01625455 NCT01738594 NCT02213861 NCT02301494 NCT02323659 NCT02448381 NCT02811783 NCT02943642 NCT02953301 NCT03011814 NCT03292406 NCT03454945 NCT03713320.

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