London Cancer
Guidelines for Cutaneous Lymphoma and Referral to Cutaneous Lymphoma Supranetwork

January 2014
Review January 2015
Version 1.0
Background

Cutaneous lymphomas are a group of disorders characterised by the localisation of malignant lymphocytes to the skin.

Approximately two thirds are of T-cell origin. The most common form of cutaneous T-cell lymphoma (CTCL) is mycosis fungoides (MF) and accounts for about 60% of cases of CTCL. Sezary syndrome (SS) accounts for about 5% of cases.

Primary cutaneous B-cell lymphomas (PCBCL) make up about 20-25% of cutaneous lymphomas in which there is no evidence of extracutaneous disease at presentation. They make up a heterogeneous group and can be classified into different subsets based on histopathological findings and clinical course.

The other 10% are made up of either very rare or currently unidentified subsets.

A fortnightly skin lymphoma clinic for referral of suspected/confirmed cases of cutaneous lymphoma operates at the Royal Free Hospital. This is led by Dr Ferina Ismail (Consultant Dermatologist), who works jointly with Dr Kate Cwynarski (Consultant Haematologist) and Dr Grant Stewart (Consultant Clinical Oncologist), with a Clinical Nurse Specialist (Alan Milligan). A similar clinic is held at Barts and the London Trust, led by Professor Harwood and Professor Cerio (Dermatology), and Dr S Montoto (Haem onc). There is close liaison with the cutaneous lymphoma supranetwork at St John’s Institute of Dermatology (Guys and St ‘Thomas’ hospitals), where complex cases are discussed and advice given or jointly managed (see appendix 1 and 2).

Cutaneous T-Cell Lymphoma

Mycosis fungoides (MF) and Sezary syndrome (SS)

MF is characterised by distinct clinical stages consisting of patches/plaques, tumours and erythroderma. SS is a distinct variant which is defined by the presence of erythroderma, peripheral lymphadenopathy and a minimum number of Sezary cells within the peripheral blood.

Diagnosis

Diagnosis is based on thorough assessment of both clinical and pathological features. Repeated biopsies may be required to establish the diagnosis and correlation between clinical features and histology is essential. This should be performed at an MDT in which dermatologists, dermatopathologists, haematopathologists, hamato-oncologists and clinical oncologists should be represented.

Staging investigations should include CT scan of chest, abdomen and pelvis, assessment of peripheral blood for Sezary cells and lymphocyte subsets, with the exception of those with early stage MF (Stage 1A/1B). Bone marrow biopsies are not required unless there is an unexplained haematological abnormality.
Staging
Two staging systems are currently in use. The tumour/node/metastasis (TNM) system and a clinical staging system specifically designed for CTCL (Bunn and Lambert).

Prognosis
Most cases of MF and SS are not curable. Independent prognostic features include the cutaneous and lymph node stage of disease and the age of onset (>60 years). Lymph node status and tumour burden within peripheral blood determine prognosis in SS. Thickness of the infiltrate in plaque stage MF, serum lactate dehydrogenase and folliculotropic variants of MF may have a worse prognosis.

Survival rates
The 5- and 10-year overall survival (os) rates in MF are 80% and 57% respectively. The disease specific survival (dss) rates are 89% and 75% respectively

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<thead>
<tr>
<th>Stage</th>
<th>os:</th>
<th>dss:</th>
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<tr>
<td>IA</td>
<td>96-100%</td>
<td>100% at 5 years</td>
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<tr>
<td>IB</td>
<td>73-86%</td>
<td>81-96% at 5 years</td>
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<tr>
<td>IIA</td>
<td>40-65%</td>
<td>50-80% at 5 years</td>
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<tr>
<td>III</td>
<td>erythroderma but no evidence of lymph node or blood involvement – survival rates similar to stage 2B disease</td>
<td></td>
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<tr>
<td>IV</td>
<td>dss 20% at 5 years</td>
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Patients with SS have an 11% 5 year survival with a median survival of 32 months from diagnosis.

Treatment of CTCL

1. Skin directed therapy

Topical therapy

For patients with early stage MF (1A/1B) emollients +/- topical steroids are often the first line treatments. Potent topical steroids can produce a clinical response although this is usually short-lived. Other treatment options include topical nitrogen mustard and topical carmustine though these latter two treatments are much less commonly used.

Phototherapy

Phototherapy is the standard of care for patients with early stages of MF. There is a high rate of complete remission and it can produce a reasonable duration of response. It is not known whether phototherapy affects time to progression and disease specific survival in those patients with early stage disease at risk of disease progression.

UVB phototherapy
Both narrowband UVB (TL-01; 311-313nm) and broadband UVB (290-320nm) phototherapy can produce high rates of complete remission with prolonged response duration, most frequently in patients with patch/thin plaque disease

PUVA photo-chemotherapy
Very high rates of complete remission have been established for PUVA in early stages of MF. Duration of response can be prolonged but does vary. Patients with erythrodermic MF can respond to PUVA but pruritus can be aggravated and it is often not tolerated. PUVA can be used as salvage therapy after other treatment for high grade disease.
Combination PUVA regimens
In patients who have shown only a partial response to PUVA or in order to reduce overall cumulative UVA dose, addition of a systemic agent may be considered.

**Radiotherapy**

MF is highly radiosensitive and localised radiotherapy (superficial orthovoltage or electrons) is used in both early and late stage disease. Over 90% of plaques and tumours resolve following superficial radiotherapy. In-field recurrences may occur for lesions treated with lower doses but use of low doses (40gy in 2-3 daily fractions at 80-120kv) allows treatment of overlapping fields and repeated treatment of difficult sites. Localised radiotherapy can also be used for isolated tumours that develop on a background of erythroderma. Superficial radiotherapy can be used for localised tumours and high doses can be used for localised peripheral nodal disease.

2. **Total skin electron beam therapy (TSEB)**

All patients to be considered for TSEB will be referred to the supranetwork MDT for discussion (appendix 1 and 2). TSEB is performed at St John's Institute of Dermatology and therefore patients are managed jointly with the cutaneous lymphoma team there. Eortc consensus guidelines for the use of TSEB in CTCL have been published (Jones et al, 2002). TSEB is highly effective but as there are other therapies with similar efficacy in early stages of disease, it is usually reserved for later stages of disease. It may be used in patients with progressive disease who have failed to respond to other therapies. TSEB may be considered as second line and sometimes first line therapy for patients with erythrodermic MF without peripheral blood involvement.

3. **Systemic biologic therapies**

**Alpha interferon**
Interferon α may be considered in patients who are failing to respond adequately to skin directed therapy or who have progressive disease. Responses are seen in early stage disease. Higher doses produce better responses but are associated with significant side effects including flu-like symptoms, lethargy and lymphopaenia, in many patients limiting dose escalation.

**Retinoids**
Bexarotene has shown significant efficacy and good duration of response with low rates of disease progression. Common side effects include significant hypertriglyceridaemia and universal central hypothyroidism which require regular monitoring, the use of Thyroxine and lipid lowering agents including a fibrate. The U.K. consensus statement on safe clinical prescribing of bexarotene for patients with cutaneous T-cell lymphoma was published this year (BJD Jan 2013)

**Denileukin Diftitox (Diphtheria IL-2 fusion toxin)**
Denileukin Diftitox is effective in heavily pre-treated patients with late stages of disease and efficacy may be improved by combining with Bexarotene. Patients to be considered for this therapy will require discussion and referral to the supranetwork site.
4. Antibody therapies

Alemtuzumab (Campath-1H – a humanised anti-cd52 antibody) has been used in small cohorts of patients with advanced disease with encouraging response rates. Response duration may be short but it remains an important 2nd and 3rd line therapeutic option for patients with advanced disease. Treatment would only be considered after involvement of the supranetwork site.

5. Extracorporeal photopheresis (ECP)

Treatment with ECP is available at the supranetwork site at St John’s Institute of Dermatology and patients to be considered for this treatment must be referred to the supranetwork MDT for discussion (see appendix 1 and 2). ECP is an effective treatment in erythrodermic CTCL with overall response rates of 35-71%.

6. Chemotherapy

Either single agent (e.g. chlorambucil, Methotrexate, Gemcitibine) or combination chemotherapy for advanced disease may be considered, again following referral for discussion at supranetwork MDT. Patients with CTCL are at high risk of septicaemia and therapy-related mortality with combination chemotherapy is a significant risk, and therefore patient’s quality of life should always be considered before giving toxic chemotherapy regimens with limited efficacy.

7. Autologous/allogeneic peripheral blood/bone marrow stem cell transplant

Autologous stem cell transplant has been performed in small numbers of patients and appears to be associated with only short term remission in the majority of patients. Eligibility of such patients would require discussion at the supranetwork MDT.

Cutaneous B Cell Lymphoma

Primary cutaneous anaplastic large cell lymphoma (pcalcl)

Pcalcl usually presents as solitary, clustered or scattered subcutaneous nodules, some of which may ulcerate. Extra-cutaneous disease is seen in about 10% of cases and mainly involves regional lymph nodes. It has an indolent course and lesions can occasionally spontaneously remit. Lesions may be seen with lesions of lymphomatoid papulosis which invariably show spontaneous remission, and the two entities are thought to be part of a spectrum of disease. The 10-year survival is 95% however multifocal lesions, particularly those appearing on the leg, are thought to have a worse prognosis. Treatment is usually excision of lesions or radiotherapy. In purely cutaneous disease chemotherapy should be avoided.

Primary cutaneous b-cell lymphoma (pcbcl)

Pcbcl represents about 20-25% of cutaneous lymphomas
There are 3 main types:
**Primary cutaneous marginal zone lymphoma (pcmzl)**
**Primary cutaneous follicle centre cell lymphoma (pcfcl)**
**Primary cutaneous diffuse large b-cell lymphoma, leg type (pcbcl –l)**

Pcmzl and pcfccl are indolent types of lymphoma which should not be treated primarily with systemic chemotherapy.

**Clinical features**

Pcmzl usually consists of solitary or multiple papules, plaques or nodules without surface scale and are preferentially located on the extremities. There is sometimes an association with Borrelia Burgdorfori infection. Cutaneous relapses are frequent but extracutaneous spread is rare.

Pcfcl usually presents with solitary or grouped tumours on the head or trunk. Cutaneous relapses occur in 20% and extracutaneous dissemination is seen in 5 – 10%.

Pcbcl-I usually presents on the legs and rarely at other sites. There are either solitary or multiple tumours with frequent relapses and extracutaneous dissemination.

**Prognosis**

Pcmzl: 5-year survival > 95%
Pcfcl: 5-year survival 95%
Pcbcl-I: 5-year survival 50%

**Diagnosis and staging of pcbcl**

When a cutaneous B-cell lymphoma is clinically suspected, adequate histopathological and immunohistochemical studies are required to confirm the diagnosis and all cases should be reviewed by an experienced dermatopathologist and/or haematopathologist within the London Cancer Network.

Staging should include a thorough clinical examination, full blood count, blood biochemistry, lactate dehydrogenase, Borrelia serology and serum electrophoresis. A CT scan of thorax, abdomen and pelvis (include neck if lesions on the head and neck), and a bone marrow biopsy should be performed to rule out systemic lymphoma.

**Treatment**

- **Primary cutaneous marginal zone lymphoma**

  **Excision**
  In patients presenting with one or a few small lesions surgical excision is the treatment of choice. There is no information as to excision margins, recurrence site or extra-cutaneous dissemination.

  **Radiotherapy**
  Pcmzl is a very radiosensitive tumour and is the treatment of choice for solitary or scattered lesions that are not small enough to excise.

  **Rituximab**
  Both systemic and intralesional rituximab have been used to treat pcmzl.

Single agent and combination chemotherapy
Multifocal disease can be treated with single agent Chlorambucil or multiagent chemotherapy, mostly with CHOP.

Antibiotics
Pcmzl associated with Borrelia burgdorffii infection should be treated with antibiotics before more aggressive therapies are used. The efficacy of antibiotic treatment in Borrelia burgdorffii-associated pcmzl is poorly documented. It is suggested that systemic treatment with cephalosporins is superior to high-dose tetracyclines

In patients with disseminated skin lesions it is acceptable to adopt a wait and see policy. These patients require careful follow-up and only symptomatic lesions should be treated. Treatment of skin lesions does not alter the prognosis and cutaneous relapse following treatment does not signify a worse prognosis.

- **Primary cutaneous follicle centre cell lymphoma (pcfcl)**

Radiotherapy
Local radiotherapy is the treatment of choice being very effective with few side effects. In patients with solitary or localised skin lesions, radiation therapy with a radiation dose of at least 30gy and a margin of clinically uninvolved skin of 1-1.5cm is the preferred mode of treatment.

Excision
Complete excision can be performed for appropriate lesions. Solitary, small, well-demarcated lesions can be excised surgically

Intralesional interferon α
There are reports of successful management of pcfcl with intralesional interferon α

Rituximab
Intralesional and systemic Rituximab have been used in pcfcl with success. In patients with very extensive skin lesions, systemic Rituximab should be the treatment of choice.

Multiagent chemotherapy
There is relatively little data available on the treatment of pcfcl patients with multiagent chemotherapy. Most patients were treated with CHOP.

Relapses occur in 30%, mostly confined to the skin and do not signify a worse prognosis.

- **Primary cutaneous diffuse large b-cell lymphoma, leg type**

Multiagent chemotherapy
R-CHOP should be the first line of treatment for pclbcl-l however many of the patients are very elderly and such an aggressive treatment may not be appropriate. These patients should be treated with local radiotherapy to all visible skin lesions. Rituximab as a single agent could also be considered.
Appendix 1: London Cancer pathway for cutaneous lymphoma

Patient referred to local dermatologist (or other specialty) by GP

Diagnosis of cutaneous lymphoma

Discussion at local skin MDT

Referral from other specialties (e.g. Haematology)

Discussion at specialist network skin MDT +/- Haematology Oncology MDT

Manage locally

Referral to / management in Network Cutaneous Lymphoma clinics

- Royal Free Hospital - Dr Ismail (Dermatology), Dr Cwynarski (Haematology), Dr Stewart (Clinical Oncology)

- Barts and the London Trust - Profs Harwood and Profs Cerio (Dermatology), Dr S Montoto (Haem onc)

Referral to Supranetwork MDT*

*Consider patient referral to supranetwork skin tumour unit (St John’s Institute of Dermatology, Guy’s and St Thomas’ Hospitals) for:

Further evaluation +/- management
All diagnoses made by LSMDT should be referred on to the SSMDT for further review and management as per IOG. The SSMDT must determine if patients need to be discussed with and/or referred on to the relevant Haematology MDT at BLT or RFH.

After discussion at SSMDT referral to supra specialist MDT at the Skin tumour Unit, St John’s Institute of Dermatology can be considered for:

- Diagnostic problems
- CTCL stage 1B and above if require decisions about treatment or opportunity to participate in a clinical trial
- Rare CTCL variants

Referral email is skintumour@gstt.nhs.uk.

MDM co-ordinator is Sarah.king-1@gstt.nhs.uk.

At all times the MDT must make the decision based on what is best for that patient and not allow undue delay in the care for that patient. If a patient is referred to another MDT, then feedback will occur so that the care of the patient is available to audit and governance.
Appendix 2: Guidelines for referral to the supranetwork MDT for consideration of photopheresis in the management of cutaneous t-cell lymphoma (CTCL)

Major criteria

Erythroderma
Stage III or IV CTCL (histology consistent with CTCL)

Minor criteria

Circulating T-cell clone
Evidence of circulating Sezary cells (>10% of circulating lymphocytes)
CD4/CD8 ratio >10

2 major and 1 minor criteria required