Cutaneous T-cell lymphoma: practical recommendations to enhance clinical practice

Abstract

Management of cutaneous T-cell lymphoma should provide a holistic approach to a patient's wellbeing. Treatments depend on the stage of lymphoma. Patients with the early stages tend to have a near-normal life expectancy. Management should be aimed at improving the extent of disease and reducing symptoms with minimal therapeutic adverse effects. Skin-directed treatments are preferred and may be used in combination with treatments for symptom relief such as anti-pruritic medication. In advanced stages of disease where the median life expectancy is reduced the aims are also to prevent disease progression and prolong life, and this requires a multidisciplinary approach. Symptom control remains important as patients often have painful, itchy disfiguring lesions which greatly impact on health-related quality of life.

National and international guidelines provide stage-related treatment options to be considered with first-line options followed by subsequent second-line therapies. All are listed in no particular order of preference and are chosen according to patients' needs and expertise of the treating centre. Several first-line options may be chosen before moving to the second-line options.

Three drugs received European Medicines Agency approval in 2017 and 2018 (chlormethine gel, brentuximab and mogamulizumab) but there still remains an unmet need for more improved treatments or combinations. Most treatments only result in a partial response and there is no cure for early-stage disease; as such, patients live for a long time with their disease. In the advanced stages if a good response is achieved eligible patients will be considered for an allogeneic haematopoietic stem cell transplant.

Key words: CTCL, cutaneous T-cell lymphoma, mycosis fungoides, Sézary syndrome, supportive care, treatment

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Introduction

The management of cutaneous T-cell lymphoma is predominantly dependent on the stage of disease but other factors that affect best management include how aggressive the lymphoma is, the patient's performance status and quality of life issues. Cutaneous T-cell lymphoma includes a number of variants, with the most common being mycosis fungoides (accounting for around 60% of cases) and Sézary syndrome (accounting for around 5%) (Willemze et al, 2019). This article focuses on the management of these more common subtypes.

Diagnosis

There is no single test for cutaneous T-cell lymphoma, making the diagnosis complex. Clinicopathological correlation is essential and requires the expertise of a specialist multidisciplinary team. Staging of mycosis fungoides or Sézary syndrome is undertaken using the TNMB (tumour, lymph node, metastasis, blood) classification and divides patients into nine stages (IA–IVB) (Table 1). Mycosis fungoides typically presents with 'early-stage' (I–IIA) skin lesions with cutaneous patches and/or plaques and may progress to 'advanced stage' (IIB–IVB) with skin tumours or erythroderma (Olsen et al, 2007). Low level blood or lymph node involvement may be present in early stages and progression to advanced stages can occur with extensive lymphomatous infiltrates in the lymph nodes, leukaemic blood involvement

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Table 1. TNMB classification for mycosis fungoides or Sézary syndrome. This divides patients into nine stages from IA–IVB: IA–IIA are designated 'early stage' and IIB–IVB the 'advanced stage'

Stage	Tumour (T)	Lymph node (N)	Metastasis (M)	Blood (B)
IA	T1: Patches/plaques over <10% of body surface T1a patches only T1b plaques only	N0: No palpable nodes or histological evidence of mycosis fungoides N0a clone negative N0b clone positive	M0: No visceral involvement	B0: <5% peripheral blood lymphocytes atypical B0a clone negative B0b clone positive B1: >5% of lymphocytes atypical but <1000/ul B1a clone negative B1b clone positive
IB	T2: Patches or plaques over >10% of body surface T2a patches only T2b plaques only	N0	M0	B0–1
IIA	T1 or T2	N1: no histological evidence of mycosis fungoides (dermatopathic) N1a clone negative N1b clone positive N2: early involvement with mycosis fungoides, aggregates of atypical cells with preservation of nodal architecture N2a clone negative N2b clone positive	M0	B0–1
IIB	T3: Tumours, lesions >1 cm diameter with deep infiltration	N0–2	M0	B0–1
IIIA	T4: Erythroderma >80% body surface area involved	N0–2	M0	B0
IIIB	T4: Erythroderma	N0–2	M0	B1: >5% of lymphocytes atypical but <1000/ul
IVA1	T1–T4	N0–2	M0	B2: >1000/ul circulating atypical lymphocytes (Sézary cells)
IVA2	T1–T4	N3: Lymph nodes involved with effacement of normal architecture	M0	B0–2
IVB	T1–T4	N0–N3	M1: Metastasis	B0–2

or metastatic spread (Willemze et al, 2019). Some patients present with the advanced stages. Sézary syndrome is defined by erythroderma and leukaemic blood involvement.

Treatment

National and international management guidelines provide treatment options for each stage of disease (Trautinger et al, 2017; Gilson et al, 2019; National Comprehensive Cancer Network, 2020). Treatments are listed as first-line options and second-line or subsequent therapies and for each line of therapy there are several choices listed in no particular order

of preference. Physicians should select the ideal therapy for each patient depending on the individual circumstance of the patient allowing personalised medicine.

There are a wide range of therapeutic options for patients with mycosis fungoides or Sézary syndrome, including skin-directed therapy such as topical, photo- and radiotherapies, systemic immunotherapies, chemotherapy and allogeneic haematopoietic stem cell transplantation. The choice of an individual or combination of treatments is based on the stage of disease. The major national (Gilson et al, 2019) and international guidelines (*European Organisation for Research and Treatment of Cancer* – Trautinger et al, 2017; National Comprehensive Cancer Network, 2020) provide treatment options for patients with cutaneous T-cell lymphoma.

Treatments are stage related and divided into first-line or upfront therapies followed by second-line or subsequent therapies. Treatments are listed in each category in no particular order of preference and several therapies from the first-line options are usually tried before moving the patient to second-line options. Treatments are decided depending on patient circumstance and expertise of the treating centre. For example, a patient living 50 miles from the centre may prefer a topical therapy applied at home compared to an in-hospital treatment like phototherapy. Treatments tend to be given consecutively until loss of response as complete responses are rare. For early-stage disease where median survival is >10 years, treatments are aimed at reducing symptoms, improving quality of life and preventing disease progression. In advanced stages more intensive treatment is aimed at reducing the tumour burden and prolonging life without negatively impacting on health-related quality of life. In eligible patients with advanced disease, allogeneic haematopoietic stem cell transplantation may be considered and could provide a cure although low grade relapse is frequent (Ritchie et al, 2020).

New therapies are being developed and this article includes the basic principles of treatments but guidelines are continually updated and should be referred to.

Early-stage mycosis fungoides (IA–IIA)

Early-stage mycosis fungoides should be managed with skin-directed therapy first line (Lovgren and Scarisbrick, 2019). This includes topical corticosteroids which provide symptomatic relief from itch, redness and inflammation but have not been proven to specifically treat malignant lymphocytes. Ultraviolet light is an effective treatment for mycosis fungoides and in sunnier climates patients may expose themselves to natural sunlight. Phototherapy in the form of ultraviolet B (narrow band 311–313 nm has generally replaced broad band) or PUVA (psoralen + ultraviolet A; 340–400 nm) are both effective therapies for patch or plaque mycosis fungoides, the latter being preferred for thicker plaques. Topical chlormethine gel 0.02% has been approved in the USA since 2017, received European Medicines Agency approval (2017) and is undergoing National Institute for Health and Care Excellence review. It is a topical nitrogen mustard agent that is effective in cutaneous T-cell lymphoma. Local radiotherapy (4–8 Gy in 1–2 fractions) is highly effective for thick plaques. For patients with widespread disease refractory to phototherapy total skin electron beam therapy may be given which allows whole body treatment (Morris et al, 2017). Low-dose total skin electron beam therapy (12 Gy in eight fractions over 2 weeks) is significantly better tolerated than standard-dose total skin electron beam therapy (30–36 Gy over 8–10 weeks) and may be repeated.

The aims of treatment are to reduce skin tumour burden, alleviate the symptoms of painful itchy skin lesions, enhance functionality if lesions are affecting daily activity (eg lesions on hands and feet) and improve emotional wellbeing, which should all improve health-related quality of life. Delaying disease progression is important but as only 25% of cases progress to the advanced stages identifying these patients and the therapeutic role in delaying disease progression is still poorly understood. An international prognostic study in patients with mycosis fungoides and Sézary syndrome (PROCLIPI) is ongoing and has shown raised serum levels of lactate dehydrogenase and thicker plaques may be indicators of likely disease progression (Scarisbrick et al, 2014, 2019).

Selecting which skin-directed therapy to use will depend on the individual being treated. A course of phototherapy requires multiple hospital visits (2–3 × week, for 8–16 weeks). There is an upper limit of phototherapy which may be safely given before the risk of other cutaneous malignancies outweighs any benefit.

Patients often cycle through various skin-directed therapies during their course of disease and may have periods during which they receive no anti-cutaneous T-cell lymphoma therapy, termed 'expectant' therapy. At any time, patients may receive symptomatic treatments to help with itch, pain, depression, insomnia or superadded infection (Trautinger et al, 2017; Scarisbrick, 2018; Gilson et al, 2019).

Some patients become refractory to skin-directed therapy and may be considered for second-line treatment options. These include bexarotene or interferon 2a. Bexarotene is an oral rexinoid (retinoid X receptor agonist) which requires lipid-lowering therapy and thyroxine replacement to be given to counteract the common side effects (Scarisbrick et al, 2013). Interferon 2a is a thrice-weekly injection that is well tolerated but can cause flu-like symptoms. Manufacture has recently been withdrawn and patients have been substituted with weekly pegylated interferon injections. Other agents include mogamulizumab (Poteligeo), a CCR4 monoclonal antibody effective against cutaneous T-cell lymphoma cells, which showed efficacy in some patients with early-stage mycosis fungoides lesions (Kim et al, 2018). It is given initially as weekly then biweekly infusion which is generally well tolerated; the main side effects are infusion-related reactions and drug eruption.

Advanced stage disease (IIB–IVB)

While advanced stages are treated predominantly with systemic therapy, skin-directed therapy still has a role for symptom relief and as adjuvant therapy. Patients with skin tumours but no or low levels of blood or lymph node involvement are stage IIB. In patient with solitary or limited tumour disease radiotherapy may be preferred. In patients with multiple tumours bexarotene, interferon 2a or total skin electron beam therapy may be used with boosters to individual tumours. Second-line choices include brentuximab (Adcetris), a monoclonal CD30 antibody conjugated to the toxin vedotin which is effective for CD30-positive mycosis fungoides (Prince et al, 2017); this received European Medicines Agency approval in 2018 and National Institute for Health and Care Excellence approval in 2019. It is an infusion given every 3 weeks. It is well tolerated but around two-thirds of patients develop a neuropathy; this tends to resolve on stopping but may limit treatment. Other options include clinical trials or chemotherapy (gemcitabine, liposomal doxorubicin, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)). Chemotherapy is often preferred in patients with extensive nodal lymphomatous involvement (IVA2) or visceral disease (IVB). These patients have a poor prognosis and median survival is around 1 year (Scarisbrick et al, 2015). Eligible patients with a good response to treatment should be considered for an allogeneic haematopoietic stem cell transplant (Trautinger et al, 2017; Gilson et al, 2019; National Comprehensive Cancer Network, 2020). Transplants have not been successful in patients with active disease (Lechowicz et al, 2014; Ritchie et al, 2020).

Patients with erythroderma are staged according to their blood tumour burden. Blood tumour burden may be calculated using flow cytometry measurements of CD4+CD7- and/or CD4+CD26- cells (Scarisbrick et al, 2018a,b). These aberrant phenotypes may be seen in benign dermatoses: an absolute count of ≤250 IU/litre is classed as B0 and in erythrodermic patients staged IIIA; while 1000 IU/litre or above is classed as B2 and in the presence of erythroderma and a peripheral blood clone identical to skin is diagnostic of Sézary syndrome (stage IVA1). Those with intermediate level blood involvement (250–<1000 IU/litre) are classed B1 and stage IIIB. Treatment of IIIA–IIIB may be with whole body skin-directed therapy (phototherapy or total skin electron beam therapy) or systemic therapies which are recommended for Sézary syndrome such as methotrexate, bexarotene, interferon 2a or extracorporeal photopheresis. Extracorporeal photopheresis has the advantage of having an excellent safety profile without an increase in immunosuppression or second malignancies seen with some other systemic therapies. It is delivered on two consecutive days every 2–4 weeks within the hospital and may be given together with bexarotene and interferon 2a as triple therapy (Alfred et al, 2017). Second-line options include mogamulizumab, which is particularly effective in reducing blood tumour burden, brentuximab (if CD30+), alemtuzumab (an anti CD52 monoclonal antibody therapy) or chemotherapy. In patients with Sézary syndrome the prognosis is poor (median survival around 3 years) and an allogeneic haematopoietic stem cell transplant should be considered in eligible patients.

Key points

- Early-stage mycosis fungoides should be treated with skin-directed therapy.
- In early-stage mycosis fungoides there may be periods of 'expectant therapy' when no treatment is preferred.
- In patients with advanced stage mycosis fungoides or Sézary syndrome, systemic treatments may be considered first line and multidisciplinary care involving dermatology and haemato-oncology is needed.
- In advanced stage disease where life expectancy may be severely reduced allogeneic haematopoietic stem cell transplantation may be considered.
- A holistic approach to patient care with consideration of health-related quality of life is essential, and symptomatic relief for pain, itch, insomnia and depression may be needed.

Conclusions

There is currently an unmet need for better therapies for mycosis fungoides and Sézary syndrome. In the last few years, three drugs have received European Medicines Agency approval (chlormethine gel, brentuximab, mogamulizumab) and been added to the repertoire of medications available to treat cutaneous T-cell lymphoma. Most drugs have low overall response rates, few complete responses and short duration of response (typically less than 1 year) and there remains an unmet need for more therapies or improved combinations of therapies. The aim of management should be discussed with the patient. In early-stage disease this is likely to be to manage symptoms and reduce tumour burden. However around 25% of patients presenting with early-stage disease will progress to the advanced stages. Identifying these patients for more intensive therapy may be beneficial and improve outcome (Mourad and Gniadecki, 2020). The PROCLIPI Study (PROspective Cutaneous Lymphoma International Prognostic Index Study) is aiming to identify those factors which may be associated with stage progression (Scarisbrick et al, 2019). The therapeutic strategy in advanced stage patients may be aimed at achieving a complete response (or near complete response) followed by allogeneic haematopoietic stem cell transplant. In those not eligible for allogeneic haematopoietic stem cell transplant, managing symptoms, reducing tumour burden and preventing progression are important.

Randomised controlled clinical trials provide an excellent opportunity for patients to be given new therapies or combinations which may not otherwise be available and allows further knowledge to be gained on treatment responses.

Throughout management of mycosis fungoides or Sézary syndrome, consideration should be given to patients' comorbidities and quality of life as cure is rarely achieved and patients may live many years with their disease.

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Conflicts of interest

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