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Mycosis Fungoides and Sezary Syndrome: Australian Clinical Practice Statement

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Mycosis Fungoides and Sezary Syndrome: Australian Clinical Practice Statement

Abstract

Primary cutaneous lymphomas represent a heterogenous group of T- and B- cell lymphomas with distinct clinical presentations, histopathologic features, treatment approaches and outcomes. The cutaneous T cell lymphomas, which include Mycosis Fungoides and Sezary syndrome, account for the majority of the cutaneous lymphomas. This Clinical Practice Statement is reflective of the current clinical practice in Australia. An expanded form of the Clinical Practice Statement (and updates), along with helpful patient resources and access to support groups can be found at the following (http://www.australasianlymphomaalliance.org.au).

Introduction

Primary cutaneous lymphomas represent a heterogenous group of T- and B- cell lymphomas. The cutaneous T-cell lymphomas (CTCL) account for up to 80% of all cutaneous lymphomas[1, 2]. They are a rare and heterogenous group of malignancies that frequently pose a diagnostic challenge. The most prevalent CTCL is Mycosis Fungoides (MF)[3]. Sezary syndrome (SS) is a variant of CTCL and is characterized by erythroderma and a leukaemic burden of circulating neoplastic T-cells. This Clinical Practice Statement is reflective of the current clinical practice in Australia and was developed utilising the Australian Lymphoma Alliance principles for Consensus Practice Statement Development. An expanded form of the Clinical Practice Statement (and updates) can be found at the following (http://www.australasianlymphomaalliance.org.au). Levels of evidence and grades of recommendation have been applied using the National Health and Medical Research Council (NHMRC) criteria (Supplementary 1).

Classification

The World Health Organisation (WHO) and European Organisation for Research and treatment of Cancer (EORTC) consensus classification for cutaneous lymphomas was originally developed in 2005, and updated in 2018, and divides the cutaneous T-cell lymphomas into indolent and aggressive forms (see Table 1)[1, 2] . MF is classified as an indolent lymphoma as per the WHO-EORTC classification, in contrast to Sezary Syndrome, which is classified as an aggressive lymphoma.

MF and its variants

Classical MF typically presents as a slowly progressive disease with a protracted evolution, characterised by erythematous patches, plaques, tumours or uncommonly erythroderma. MF often evolves in sun-protected sites, referred to as ‘bathing trunk distribution’. In most patients the disease is limited to cutaneous patches or plaques, with an estimated 5 year survival rate of >80% (see Table 2) [4]. However, 20% of patients may develop cutaneous or extracutaneous tumours with

an estimated 5-year survival rate of approximately 40% (see Table 2) [5] . There are three clinicopathological variants with variable prognosis listed in the EORTC-WHO consensus statement: folliculotropic MF, granulomatous slack skin, and pagetoid reticulosis. There are multiple other clinicopathological variations of MF but these do not appear to influence prognosis[2].

Sezary Syndrome

Sezary syndrome is defined according to the WHO criteria by the presence of erythroderma, peripheral lymphadenopathy and Sezary cells comprising > 1 x 10^9/L (1000 cells/mm^2), the latter often demonstrating a CD4:CD8 ratio > 10, or aberrant expression of pan T-cell markers[2]. An identical T-cell clone may be seen in the blood and skin, however, it can be technically difficult to demonstrate a clone on skin biopsies. It can arise de novo or, less commonly, as a progression of pre-existing MF (erythrodermic MF). It is not uncommon for skin biopsy changes in Sezary syndrome to be relatively non-specific.

Diagnosis

The diagnosis and classification of cutaneous lymphoma is based on both clinical and pathological features. Ideally all patients with MF/Sezary Syndrome should be evaluated, and those with advanced stage disease co-managed, by a multidisciplinary cutaneous lymphoma team consisting of dermatologists, pathologists, radiation oncologists, and haematologists, together with the support of other healthcare professionals such as nurse specialists and clinical psychologists[6].

Routine initial evaluation should include (see Table 3) a complete physical examination, including assessment for lymphadenopathy.

Blood tests: We recommend blood tests be undertaken in all patients with Stage 1B disease or greater. This should include a basic haematological and biochemistry panel including complete blood count with differential, peripheral blood film for Sezary cell count, calcium, magnesium and phosphate, lactate dehydrogenase (LDH), and Beta 2 microglobulin. Flow cytometry of blood should be performed to identify two abnormalities; i) an elevated CD4;CD8 ratio and/or ii) immunophenotypic aberrancy (ie Sézary cells). T-cell receptor (TCR) gene rearrangement studies need to be considered on both tissue and blood to check for a matching clone. This is not commonly recommended in early stage disease as it does not influence treatment and is often undetectable due to low tumour load. It should be considered in patients with high risk of blood involvement (T2 and beyond). TCR gene studies are usually performed in a tertiary hospital setting due to the significant

expense to patients in the community as it is not funded by the Medicare Benefits Scheme. Additionally, serology for Human T-lymphotropic Virus 1 (HTLV1), to exclude adult T-cell leukaemia / lymphoma which may mimic CTCL, and pre-treatment screening investigations for HIV serology, Hepatitis B and C serology and Cytomegalovirus (CMV) serology should be considered.

Skin biopsy for histology and T-cell rearrangement studies: In order to establish the nature of the disease process over the course of the disease, multiple skin biopsies are often required, the number, size and quality of which are integral in enabling early diagnosis. Ideally three, 3mm punch biopsies should be undertaken at the initial presentation, while consideration should be given to an incisional biopsy to enable ancillary testing in addition to histology. Biopsies should ideally be untaken from different sites if various morphologies of MF are present.

Establishment of a T-cell Clone: The presence of an aberrant T-cell population and/or clone is an important diagnostic criterion. Aberrancy can be determined by i) immunohistochemistry (IHC) on skin (or node) biopsies, or ii) flow cytometry of blood or skin. Testing for T-cell receptor clonality can be done by molecular testing on paraffin or fresh tissue or blood, and potentially by flow cytometry assessment of T-cell receptor β chain constant region 1 (TRBC1).

Staging

Clinical Staging of MF/Sezary Syndrome is outlined in Supplementary Tables 2 and 3. Accurate staging is essential for both prognostication and to guide treatment decisions. It encompasses the extent of skin involvement (T), presence of lymph node (N) and visceral disease (M), and detection of Sezary cells in the peripheral blood (B)[7] (see Supplementary Tables 2 and 3).

Radiological investigations: Radiological staging investigations are undertaken in patients at the time of diagnosis with the exception of those with Stage IA/IB MF. Imaging for advanced stage disease includes whole body Positron emission tomography – computed tomography (PET-CT) scan where available, or CT of the neck, chest, abdomen and pelvis.

Lymph Node Biopsy: Peripheral lymphadenopathy is rare in early stage disease. In advanced disease, nodes may be enlarged due to the presence of disease and/or non-specific secondary dermatopathy. Core or excisional biopsies are required to provide an accurate pathologic assessment. Histologic classification of lymph node involvement is used as a prognostic marker and to guide treatment decisions in patients diagnosed with MF/Sezary Syndrome.

Bone Marrow: Bone marrow aspirate and trephine biopsies are usually not required in early stage disease unless there are atypical clinical or haematological abnormalities that would suggest marrow involvement.

Prognostic Markers

Prognosis is largely based on stage of the disease at diagnosis, along with other adverse prognostic factors for progression and survival. For early stage disease, these include male sex, age > 60 years, presence of plaques, histological evidence of folliculotropic disease and palpable or histologically confirmed dermatopathic lymph nodes.

For late stage disease, the presence of nodal involvement, blood and visceral disease are additional important adversely prognostic features[8, 9]. In addition, several independent adverse prognostic factors have been identified including large cell transformation, thickness of tumour infiltrate, increased LDH, and elevated beta-2 microglobulin[8, 10, 11] .

Patients with large circulating Sezary cells were also found to have a worse prognosis. A high Sezary cell count, high LDH, loss of T-cell subset markers such as CD5 and CD7, and chromosomal abnormalities in T-cells are also independently associated with a poor outcome[12] .

Management

The management strategy needs to be individualised and depends of the extent of disease (TNMB stage) and its impact on a patient's quality of life. There are currently no curative treatments. Patients with early stage disease have a favourable prognosis and for most, MF is an indolent chronic disease. Those with advanced stage disease often have a more unpredictable clinical course, and multidisciplinary input can be invaluable in supporting these patients through their treatment.

We have summarized the treatment options below. First line options are labelled with an asterisk(*). Treatments that are not currently available on the Australian Pharmaceutical Benefits Scheme (PBS) are labelled with NA (not available) superscript.

Skin care and infection debulking regimens

Skin care and infection debulking regimens may benefit patients based on their stage of disease, skin integrity, pain, and pruritus scores. Multidisciplinary team (MDT) involvement as well as referral to consultative teams such as Pain and Palliative Care Services, Psychology and Psychiatry for management of intractable pruritus, skin pain and emotional implications of the disease, can be highly beneficial.

General Skin Care Measures: Bath oils and soap free washes are recommended. Specific clothing or situations that may trigger a skin flare, pruritus or pain/ sensitivity should be avoided. These include changes in temperature, fragrances, and preservatives in topical preparations. Erythrodermic patients may have difficulty regulating their body temperature and should therefore avoid extremes of temperature.

Dressings for tumours and open wounds: Selection of dressings often depends on availability and affordability of a product, disease status, symptoms, and tolerability of dressings. Patients should be encouraged to partake in their overall skin care as it assists in encouraging their self-care and feeling of control over the disease.

Infection Debulking Regimens: Infection can be a challenge and may aggravate the patients underlying cutaneous lymphoma[13]. The use of diluted Sodium hypochlorite (bleach) baths, salt baths or the topical dilute vinegar may reduce the infection load on the skin during a flare. Bleach baths incorporate 12 mls of White King Bleach per 10 L of tepid water or ¼- ½ cup in a full adult bath (Royal Children's Hospital consensus statement). One to two capfuls of bath oil may be added to combat the drying effect that bleach can have on the skin. If flares are confined to certain areas such as hands or feet, soaks may be easier to administer than a full body bath. Commercially available antimicrobial washes may be of benefit to patients who do not have access to a bathtub or have limited mobility.

Symptom Management, including Pain relief and Pruritus optimisation: Patients may require hospitalisation for management of skin flares. Intravenous antibiotics and management of pain and pruritus are often delivered together with wet dressings. Wet dressings also known as wet wraps, and can be utilised to help reduce skin inflammation and ease pruritus [14]. An alternative to wet wraps is the "Soak and Smear regimen"[15] . It involves soaking in a bathtub with lukewarm water for 20 minutes followed by application of a topical steroid ointment to wet skin. Pain relief is imperative in order for patients to carry out skin cleansing regimens and wound care, and

involvement of the Pain Team should be considered. Menthol creams and general emollients can assist in pruritus management along with systemic agents.

Treatment of Early Stage Disease (Stage IA/IB/IIA)

Early stage MF has a favourable prognosis. Those who are asymptomatic have a 10% risk of progression within 10 years with near normal life expectancy[1]. It is important to advise patients of this, so to alleviate some of the anxiety that may arise from the diagnosis. Skin directed therapies (SDT) are the mainstay of treatment in this group[16]. These involve topical therapies including corticosteroids (rarely topical chemotherapy, bexarotene^{NA}), light therapy including phototherapy, localised radiotherapy, and total skin electron (TSE) therapy. Systemic therapy is considered for patients who fail front-line SDT.

*First line treatment: Topical Corticosteroids [Level 2A evidence; Grade A]

*Very potent (class 1) topical corticosteroids are important in this group of patients. These may induce clearing of skin lesions in those with limited patches (stage 1A) and as an adjunctive therapy to decrease erythema, scaling, and pruritus. In an investigational trial, 79 patients were treated daily with topical class 1 to class 3 steroids. Thirty-two (63%) of stage T1 patients and seven (25%) of stage T2 patients achieved complete clearing. In that study, 13 patients (40%) with stage T1 and 2 patients (29%) with stage T2 relapsed, however, the median observation time was only 9 months[17].

Efficacy of topical agents can be increased by the use of wet wraps or occlusion. Common agents used include Betamethasone diproprionate 0.5 mg/g (Diprosone OV) ointment and Clobetasol Proprionate 0.05% ointment (latter currently needs to be compounded in a dedicated pharmacy).

First line treatment: Topical Chemotherapy [Level 2A evidence; Grade A]

These are generally only useful for patients with small body surface area (BSA) involvement because of the potential for systemic absorption. These include topical nitrogen mustard 0.1% to 0.2% in an aqueous or ointment base (requires compounding in a dedicated pharmacy) and topical carmustine (BCNU) (requires compounding in a dedicated pharmacy and is now difficult to source).

First line treatment: Other Topical Therapies with limited data [Level 3 evidence; Grade C]

These include imiquimod 5% cream, 5-fluorouracil cream, tretinoin 0.1% cream, and tacrolimus 0.1% ointment. Topical bexarotene 1% gel is not generally available in Australia. [Level 2A evidence; Grade A]

*First line treatment: Phototherapy [Level 2A evidence; Grade A]

*Phototherapy is a widely utilised therapeutic option and one of the mainstays of skin-directed regimens in CTCL[18-28]. Narrowband ultraviolet therapy (NBUVB) of 311-313 nm can produce high complete response rates. These complete responses are more commonly seen in patients with only patch stage disease[24-26, 29, 30] .

Psolaren-ultraviolet A photo chemotherapy (PUVA) has been shown to result in high complete response rates in early disease, however, long term risks of chronic photo-damage and secondary skin malignancy, usually outweigh the benefits of prolonged maintenance treatment. Indeed, current recommendations suggest treatment should be limited to 1200 Jcm2 or 250 sessions [31, 32]. Combination with both subcutaneous interferon and oral acitretin have been shown to reduce the cumulative UVA exposure, with interferon demonstrating improved duration of response compared to PUVA alone[33-35].

*First line treatment: Localised Radiotherapy [Level 2B evidence; Grade A]

*MF is exquisitely sensitive to radiotherapy and high response rates are expected from relatively low skin doses. Low dose, localised radiotherapy (8-12 Gy) is often favoured for high response rate, reduced toxicities and ease of re-irradiation if required. Dose-response to radiotherapy is reported: doses > 8 Gy achieve complete responses rates exceeding 90%[36, 37] Localised radiotherapy can also be used conjunctively with topical therapies and phototherapy.

*For patients with patients with a solitary patch or plaque, higher doses of localised radiotherapy (24-30 Gy) are associated with long-term disease control and may be curative.[38]

*First line treatment: Total Skin Electron Therapy [Level 2B evidence; Grade A]

*Total skin electron (TSE) therapy may be considered first line in patients with extensive skin-confined disease, or second line in patients with cutaneous disease that is refractory to other skin directed therapy (see relevant section below). Published data confirm greater response rates from

higher doses, with complete response rates > 80% expected from conventional-dose TSE (30-36Gy) [39, 40]. Earlier delivery of conventional-dose TSE in the treatment paradigm is associated with a more durable clinical benefit and a longer treatment-free interval[41]. However, low dose TSE (10-12 Gy) may be favoured as a well tolerated treatment with lower risks of toxicities, acceptable response rates, and ease of re-irradiation if required.[42] TSE doses <10Gy are associated with inferior response rates and are not recommended[43-45].

First Line treatment: Retinoids [Level 1B evidence; Grade A]

Acitretin, which binds to the retinoic acid receptor (RAR), has been evaluated in a few studies, however, is not frequently used as monotherapy. One retrospective study which included 32 patients with MF/Sezary Syndrome, demonstrated a 59% overall response rate, however the results are likely to be confounded by other concomitant treatments[46]. When used as monotherapy in 6 of the patients, the clinical response was seen in approximately 25%[46]. It may be particularly helpful in hyperkeratotic and palmoplantar disease. When used in combination with PUVA, it can reduce the cumulative UVA dose[33-35]. Bexarotene^{NA} is a retinoid that binds exclusively to the retinoid X receptor (RXR). It has been used overseas but is not currently available in Australia.

Refractory Disease

Systemic treatments (potentially in combination with skin directed therapy), may be considered in patients who are refractory to skin directed therapy alone. These agents can be combined with phototherapy and include subcutaneous interferon-alpha, low dose oral methotrexate, or histone deacetylase (HDAC) inhibitors (oral vorinostat, intravenous romidepsin^{NA}). (see below)

Treatment of Advanced-Stage Disease: Stage IIB (T3)

This subgroup of patients has a poor prognosis with an unpredictable clinical course, with some patients developing small and infrequent tumours, while others may develop extensive bulky skin tumours and rapidly progressive disease.

Stage IIB (T3): First Line Treatment - Skin Directed Therapy

Skin directed therapy is used as an adjunct to systemic treatments. There is no evidence that topical therapies impact long term prognosis, however, they are important to help alleviate skin symptoms such as pain and pruritus. Wet wraps or occlusion dressings with very potent (class 1) topical corticosteroids are generally recommended. Patients with co-existing patches and plaques may benefit from phototherapy if individual tumours have responded to other treatment modalities.

*Stage IIB (T3): First Line Treatment - Interferon [Level 2A evidence; Grade A]

*The use of subcutaneous interferon-alpha is recommended as a front-line therapy. Its use is mainly limited due to its adverse effects and tolerability. Interferon alpha-2A (production of which will likely cease in late 2020) and Peginterferon alpha-2A are available in Australia. The recommended doses are listed below:

- Interferon alpha-2A (Roferon): 1.5-3 MU 2nd daily to daily.
- Peginterferon alpha-2A (Pegasys): 45 – 180 ug weekly.

Responses are dose-dependent, and complete responses are rare. Studies have shown overall response rates of > 50% and complete response rates of > 20%. Response rates appear to be higher in early stage disease treated with higher doses. It is generally given as long-term therapy[47-49] and often continued once the patient is in clinical remission. The main side effects are fatigue, anorexia, and mood changes especially in older patients. Monitoring for cytopenias and thyroid disturbance is mandatory.

*Stage IIB (T3): First Line Treatment - Methotrexate [Level 1B evidence; Grade A]

*Low dose oral methotrexate (10-50 mg/week) can be considered because of good tolerance, however, a recent phase 3, multicentre trial comparing brentuximab vedotin (BV) or physicians choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA study) with methotrexate (or bexarotene) as the comparator arm, demonstrated a low response rate of 10-15% and low progression free survival of 3.5 months in the methotrexate treatment arm [50]. Oral methotrexate has been used in all stages of MF including those with large cell transformation and advanced-stage MF. Side effects include gastrointestinal symptoms, and, less commonly, oral mucositis/ stomatitis, bone-marrow suppression and hepatotoxicity.

Stage IIB (T3): First Line Treatment - Chlorambucil [Level 3 evidence; Grade B]

Oral chlorambucil can be used as alternative to Methotrexate but has a low response rate. It can be administered as low dose continuous (2-4 mg/day) or as pulse dosing as used in chronic lymphocytic leukemia (consult with specialist haematologist)

*Stage IIB (T3): First Line Treatment - Localised radiotherapy [Level 3 evidence; Grade A]

*Localised radiotherapy is often favoured for rapid tumour response and a well-tolerated toxicity profile. Localised radiotherapy provides excellent palliation of symptomatic sites of MF. Lower radiotherapy doses (8-12Gy) usually achieve high response rates, lower toxicity risks and allow for re-irradiation, if required. However, higher doses may be required for tumours. Hypofractionation (3-5 Gy per fraction) is usually well tolerated, but consideration must be given to sites of re-

irradiation, volume of skin irradiated and cosmetically sensitive areas; in these cases, smaller fraction sizes are preferred.

*Stage IIB (T3): First Line Treatment - Total Skin Electron Therapy (TSE) [Level 2A evidence; Grade A]

*For patients with skin-confined disease, conventional-dose TSE (30-36 Gy, in 1-1.5 Gy per fraction) is associated with high overall response rates. Due to the relatively shallow dosimetry of TSE, tumours must first be de-bulked with localized radiotherapy prior to commencement of TSE. Early delivery of conventional dose TSE is associated with improved durability of clinical benefit, with longer clinical benefit observed in patients with exposure to only 0-2 previous lines of therapy[41]. Low-dose TSE is increasingly used in current clinical practice[45]. Recent prospective studies report acceptable overall response rates and low rates of acute skin toxicity from low-dose TSE (10-12Gy), with ease of repeat treatment if required[51-53]. TSE doses <10Gy are associated with inferior response rates and are not recommended[43-45].

Stage IIB (T3): First Line Treatment - Chemotherapy [Level 2A evidence; Grade B]

*Chemotherapy is reserved for patients with advanced stage disease or disease considered refractory to skin directed therapy or immunobiologic agents. However, chemotherapeutic agents usually only achieve short responses that last 2-6 months. Chemotherapy is used with palliative rather than curative intent. Overall survival rates remain unchanged for more intensive regimes, and toxicity may be considerable. Single agent regimens appear to have similar efficacy to combination regimens but with lower toxicity, and therefore are preferable as palliative therapy in late stage MF and Sezary Syndrome. Durable responses with single or multi-agent regimens are rare. Multiagent chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) is generally not recommended as the response rates are no higher than single-agents and have poor durability.

The preferred agents are:

- Gemcitabine, with or without Vinorelbine.
- Pralatrexate.
- Doxorubicin.
- Cladrabine.

Stage IIB (T3): Second Line Treatment - Histone deacetylase inhibitors [Level 2A evidence; Grade A]

Histone deacetylase inhibitors (HDACi) (vorinostat and romidepsin[NA]) are typically utilised as second-line therapies. Patients need to have received systemic treatment with chemotherapy to be eligible for the drug on the Pharmaceutical Benefits Scheme (PBS). They have good long-term safety and tolerability profiles.

A phase 2 trial of vorinostat 400 mg PO daily showed a partial response in 22 (29.7%) of 74 patients with only 1 complete response [54] . One study demonstrated significant improvement in pruritus in 43% of patients and hence a marked improvement in their quality of life. Approximately 10-20% can have remissions beyond 12 months[55]. A recent international, open-label, randomized, controlled phase 3 trial comparing mogamulizumab to vorinostat in 372 patients with previously treated MF/Sezary Syndrome (MAVORIC study), demonstrated more modest results with a progression free survival of 3.1 months and a response rate of just 5% in the vorinostat group[56]. The most common serious toxicities were thrombocytopenia, anaemia, dehydration, nausea/vomiting, hypotension, infection, sepsis, pulmonary embolism, and deep venous thrombosis. These were generally reversible on discontinuation of the drug.

Romidepsin[NA] is administered intravenously as a weekly dose of 14 mg/m^2 for 3 weeks with 1 week off. Treatment is continued until intolerance or disease progression. Two phase 2 trials which evaluated romidepsin in advanced-stage MF, reported an overall response rate of 36% with a median duration of response of 15 months. Romidepsin showed prolonged clinical responses in patients with Sezary Syndrome and blood involvement[57, 58] . Significant pruritus reduction was reported in treated patients, however, this did not correlate with clinical response

Stage IIB (T3): Second Line Treatment - Brentuximab vedotin (BV) [Level 1B evidence; Grade A]
Brentuximab vedotin is an anti-CD30 monoclonal antibody-drug conjugate and is effective in patients with advanced stages of MF/Sezary Syndrome. The ALCANZA Phase 3 multicentre trial has demonstrated an overall response rate of approximately 75% and a median progression free survival of 16.7 months and superiority over methotrexate and bexarotene [50]. The PBS requires > 3% CD30 expression of lymphocytes. The quantitative evaluation of CD30 can be difficult and sometimes requires the input of expert pathologists. Brentuximab vedotin is only available through the PBS for one course after the patient has received prior PBS funded therapy. There is no PBS subsidy for re-treatment at disease progression.
Peripheral neuropathy is a common side effect, but may reverse on drug cessation or dose delay. Other side effects include fatigue, nausea, alopecia, and neutropenia.

Stage IIB (T3): Second Line Treatment - Alemtuzumab [Level 3 evidence; Grade B]

Alemtuzumab is a humanised IgG1 monoclonal antibody that targets the CD52 antigen expressed on normal and malignant B cells and T-cells, but not on haematopoietic stem cells. It may be used as a second line agent or beyond. It is generally more effective in Sezary Syndrome than MF. Reported overall and complete response rates are high, but typically responses are short lived with only a minority of responses lasting longer than 12 months. Hence, alemtuzumab can be used as a bridge to allogeneic haematopoietic stem cell transplantation (HSCT, see below). There is a high risk of infective complications; routine prophylaxis with an azole plus Bactrim DS, and valaciclovir is recommended[59].

*Stage IIB (T3): Second Line Treatment - TSE [Level 2A evidence; Grade A]

*As per: Stage IIB (T3): First Line Treatment - Total Skin Electron Therapy (TSE)

Stage IIB (T3): Second Line Treatment - Retinoids [Level 1B evidence; Grade A]

As per First Line Treatment - Early Stage Disease (above).

Stage IIB (T3): Second Line Treatment - Haematopoietic stem cell transplant (HSCT) [Level 2A evidence; Grade C]

Allogenic HSCT is the only currently available therapy with curative potential[60, 61]. Durable remissions have been reported in the two largest studies with follow up of 5- 7 years from the Centre for International Bone Marrow Transplantation Research (CIBMTR) and European Bone Marrow (EBMT) Registry; progression free survival of 17-32% and overall survival of 30 -44% at 5 years[62-64]. Improved outcomes have been noted if patients undergo HSCT earlier in the disease course and with a low burden of tumour [63, 65, 66]. For maximal reduction in disease burden prior to allogenic HSCT, conventional dose TSE prior to transplant appears to have a beneficial impact on outcomes, as seen in a single institution study suggesting that it may be particularly effective in patients with Sezary Syndrome [67, 68]. The presence of large cell transformation has a significant negative impact on the outcomes of allogeneic HSCT[60]. Despite its curative potential, treatment related mortality stands at 25% [6] and hence patient selection, taking into account age and comorbidities, is important.

Treatment of Stage III/IVA Erythrodermic MF and Sezary Syndrome

This is a poor prognosis subset however survival has improved with increasing use of immune-based therapy (ie. interferon, ECP) and less use of chemotherapy. First line options are labelled with an asterisk*.

*Treatment of Stage III/IVA Erythrodermic MF and Sezary Syndrome – Extracorporeal Photophoresis (ECP) [Level 2A evidence; Grade A]

*Extracorporeal photopheresis has shown to produce high response rates in patients with stage III-IV1 MF/Sezary Syndrome. Patients must have a circulating clone. There is no role for ECP outside these indications. It should be commenced as early as possible in the treatment paradigm. Frequency of treatment varies between centres. In Australia it is usually given every 4 weeks. ECP should be continued until a loss of response is noted.

A recent Australian retrospective study evaluated 65 patients with a diagnosis of Sezary syndrome or erythrodermic MF with blood involvement, who were treated with a novel ECP regimen of one day of treatment a week for 6 weeks, then every fortnight for 12 weeks, then monthly thereafter for at least 6 month. This study demonstrated a predicted overall survival of 120 months[69] . Early commencement of ECP at treatment lines 1-3 yielded a time to next treatment (TTNT) of 47 months with a median follow up from diagnosis of 48 months. The majority of patients (88%) commenced ECP at treatment lines 1-3 either as monotherapy or in conjunction with other systemic agents. The use of ECP alone resulted in a significant longer median TTNT[69]. Patients may benefit from combination regimens with other systemic therapies. As of October 2019, ECP has been approved by the TGA but yet to achieve re-imbursement. As such, it is only available at the Victorian Comprehensive Cancer Centre (VCCC) in Melbourne.

Treatment of Stage III/IVA Erythrodermic MF and Sezary Syndrome – Other treatments [Level 2A evidence; Grade A]

Treatment options include:

- *Interferon-alpha (see above).
- HDACi (see above).
- Low dose methotrexate or chlorambucil (see above).
- *Brentuximab vedotin (see above).
- *Alemtuzumab (see above).
- *Chemotherapy agents (see above).

- *TSE (see above) is generally not recommended in Sezary Syndrome due to very short lived duration of clinical benefit[41]. TSE with ECP has been reported with promising results in patients with erythrodermic MF[70].
- AlloSCT (see above) appears to be particularly effective for Sezary syndrome. Pre-transplant TSE allows for maximal disease control prior to allogeneic HSCT[71].

Treatment of Stage IVA2 / IVB MF/Sezary Syndrome

This is a rare but very poor prognosis subset. First line options are labelled with an asterisk* Topical potent corticosteroids have a role to play in managing symptoms as per stage IIB MF. PUVA can be used as salvage therapy since patients with advanced disease often relapse or have persistent low-grade disease post systemic treatments.

Treatment options include:

- *Interferon-alpha (see above).
- *Chemotherapy (see above).
- Histone deacetylase inhibitors (*vorinostat and romidepsin[NA]) (see above).
- *Brentuximab vedotin (see above).
- *Alemtuzumab (see above).
- Localised radiotherapy can also be considered for symptomatic and/or refractory sites of skin, nodal or visceral involvement. Relatively low doses, or single fractions, can provide effective palliation and should be considered.
- TSE can be used in combination with systemic therapies in patients with symptomatic skin disease.
- AlloSCT (see above). Pre-transplant TSE allows for maximal debulking prior to allogeneic HSCT[71].

Emerging Novel Therapeutics

The majority of these agents are not yet widely available in Australia.

Mogamulizumab[NA] [Level 1B evidence; Grade A]

Mogamulizumab is a humanised monoclonal antibody against CC-chemokine receptor 4 (CCR4). CCR4 is expressed on Tregs and T helper memory cells and plays an important role is skin homing[56]. More recently an international, open-label, randomized, controlled phase 3 trial comparing mogamulizumab to vorinostat in 372 patients with previously treated MF/Sezary Syndrome (MAVORIC study) was published. Patients with relapsed or refractory MF or Sezary

Syndrome, who had failed at least one previous systemic therapy and had an Eastern Cooperative Oncology Group (ECOG) performance score of 1 or less were recruited and randomly assigned to mogamulizumab (1.0 mg/kg weekly IV for the first 28 day cycle, then days 1 and 15 on subsequent cycles) or vorinostat (400 mg PO daily). The study demonstrated that mogamulizumab significantly prolonged progression-free survival compared with vorinostat with a median of 7.7 months in the mogamulizumab group compared to 3.1 months in the vorinostat group[56]. Using global response criteria, the response rate was 28% for mogamulizumab compared to a modest response rate of 5% in the vorinostat group. The Overall Response Rate (ORR) for patients with Sezary Syndrome assigned to mogamulizumab was 37%. Furthermore, a compartmental response in blood of 68% was demonstrated for patients (with MF or Sezary Syndrome) assigned to mogamulizumab. Side effects were manageable with the most common toxicities being grade 1-2 infusion-related reactions (32%) and drug eruptions (20%) which were typically grade 1-2. The most common serious adverse effects of any cause in the mogamulizumab group were pyrexia in 8 (4%) patients and cellulitis in 5 (3%) patients[56]. We would anticipate that mogamulizumab would have a valuable role in both Sezary Syndrome and MF as second-line therapy and beyond.

Immunomodulatory agents[NA] [Level 2A evidence; Grade B]

Lenalidomide (CC-5013), an oral immunomodulatory thalidomide analogue, is currently being used in clinical trials to treat various haematologic malignancies and solid tumours. It was recently evaluated as a single agent for advanced, refractory MF/Sezary Syndrome in an open-label phase 2 trial and achieved an overall response rate of 28% with median overall survival and progression free survival of 43 months and 8 months, respectively[72] .

Immune checkpoint inhibitors[NA] [Level 4 evidence; Grade D]

Programmed death 1 (PD-1) protein, a T-cell co-inhibitory receptor, and the PD-ligand 1 (PD-L1) play a critical role in the ability of tumour cells to evade anti-tumour activity. Immunotherapy with the PD-1 inhibitor (pembrolizumab) showed encouraging responses in patients with advanced stage MF/Sezary Syndrome[73] . Results of a multi-centre phase 2 trial included 24 patients with advanced, heavily pretreated MF/Sezary Syndrome treated with pembrolizumab at 2 mg/kg every 3 weeks for up to 2 years and showed an overall response rate of 38% (1Complete response, 8 partial response) and progression free survival of 69% at 1 year[73].

Conclusion

Making the diagnosis of CTCL can be challenging and is based on the combination of clinicopathological criteria. A multidisciplinary approach is critical for both diagnosis and patient management. MF/Sezary syndrome is generally incurable and the primary aims of treatment are symptom control and remission induction. Management options are diverse, varying from expectant through to aggressive treatments. A stage-based approach is the backbone of management strategies, with early-stage / skin-confined disease usually requiring skin-directed treatments (i.e. topical therapies, narrowband ultraviolet therapy, TSE or localised radiotherapy) and advanced stage disease commonly necessitating systemic therapy. There are a number of new potential therapeutic options on the horizon and it is hoped that these agents will bring improved outcomes for the patients.

Table 1: The World Health Organisation (WHO) and European Organisation for Research and Treatment of Cancer (EORTC) Consensus Classification

Cutaneous T-cell lymphoma

Indolent clinical behaviour
• Mycosis fungoides (and variants)
• Primary cutaneousCD30+ lymphoproliferative disorder
  • anaplastic large cell lymphoma
  • lymphomatoid papulosis
• Subcutaneous panninculitis-like T-cell lymphoma
• Primary Cutaneous CD4+ small/medium pleomorphic T-cell lymphoproliferative disorder
• Primary cutaneous acral CD8+ T-cell lymphoma
• Hydroa vacciniforme-like lymphoproliferative disorder

Aggressive clinical behaviour

- Sezary syndrome
- Extranodal natural killer/ T-cell lymphoma, nasal type
- Primary cutaneous aggressive epidermotropic cytotoxic CD8+ T-cell lymphoma
- Primary cutaneous gamma/delta T-cell lymphoma
- Primary cutaneous peripheral T-cell lymphoma, unspecified

Table 2: Survival outcomes based on Clinical Stage

		Overall Survival %		Disease Free Survival %		Progression-free survival %	
Stage		5year	10 year	5year	10year	5year	10year
IA	T1A	97	91	100	96	95	91
	T1b	91	80	96	92	88	82
IB	T2a	85	75	90	82	85	72
	T2b	81	64	86	72	75	56
IIA		78	52	89	67	83	67
IIB		40-65	34	50-80	42	52	42
IIIA		47	37	54	45	47	38
IIIB		40	25	48	45	18	27
IVA1		37	18	41	20	38	17
IVA2		18	15	23	20	23	20

IVB		18	-	18-20	-	18	-

Table 3: Baseline Investigations

Baseline Investigations
Complete Physical Examination
Blood Tests
FBE and differential
Blood film
UEC
LFT
LDH

Calcium, Magnesium, Phosphate
Flow cytometry
B2 microglobulin
Peripheral smear for Sezary cell count
CD_4:CD8 ratio
Degree of CD_{30} expression
T cell gene rearrangement study (T2 onward)
HTLV-1 serology
CMV serology
Hep B serology
Hep C serology
HIV serology
Skin Biopsy (punch biopsy or incisional biopsy)
Histology (Formalin-fixed paraffin-embedded)
T cell rearrangement (TCR) on FFPE sample
Flow cytometry (fresh sample in saline soaked gauze)

Supplementary One – NHMRC Guidelines

Levels of Evidence	
1A	Evidence from meta-analysis of randomised control trials.
1B	Evidence from at least one randomised controlled trial.
2A	Evidence from at least one well-designed non-randomised trial, including phase II trials and case-control studies.
2B	Evidence from at least one other type of well-designed, quasi-experimental study such as observational studies.
3	Evidence from well-designed non-experimental descriptive studies.
4	Evidence obtained from expert committee reports or opinions and/or of respected authorities
Grades of Recimmendations	
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Supplementary Two: TNMB Staging

T (skin)	
T1	Limited patch/plaque <10% of total body surface area
T2	Generalised patch/plaque ≥10% of total body surface area
T3	Tumour(s)
T4	Erythroderma
N (lymph node)	
No	No clinically abnormal peripheral lymph nodes
N1	Clinically abnormal peripheral lymph node, histologically uninvolved
N2	Clinically abnormal peripheral lymph node, histologically involved with nodal architecture unaffected
N3	Clinically abnormal peripheral lymph node, histologically involved with nodal architecture partially affected
NX	Clinically abnormal peripheral lymph node, no histological confirmation
M (viscera)	
Mo	No visceral involvement
M1	Viceral Involvement
B (blood)	
Bo	No circulating atypical (Sezary) cells or <5% of lymphocytes
B1	Low blood tumour burden, ≥ 5% of lymphocytes are Sezary cells, but not B2
B2	High blood tumour burger, ≥ 1000 Sezary cells/mm2 and positive clone

Supplementary Three: Clinical Staging of MF/SS

IA	T_1	N_0	M_0	B_{0-1}
IB	T_2	N_0	M_0	B_{0-1}
IIA	T_{1-2}	N_{1-2}	M_0	B_{0-1}
IIB	T_3	N_{0-2}	M_0	B_{0-1}
III	T_4	N_{0-2}	M_0	B_{0-1}
IVA_1	T_{1-4}	N_{0-2}	M_0	B_2
IVA_2	T_{1-4}	N_3	M_0	B_{0-2}
IVB	T_{1-4}	N_{0-3}	M_1	B_{0-2}

References

1. Willemze, R., et al., *The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas.* Blood, 2019. **133**(16): p. 1703-1714.DOI: 10.1182/blood-2018-11-881268 [doi].
2. Willemze, R., et al., *WHO-EORTC classification for cutaneous lymphomas.* Blood, 2005. **105**(10): p. 3768-3785.DOI: 2004-09-3502 [pii].
3. Querfeld, C.P.H.M.R.S.T., *Cutaneous T-cell lymphomas: Mycosis Fungoides and Sezary Syndrome. A Guide for the Practicing Oncologist*.

4. P.Quaglino, H.P., R.Cowan, M.Vermeer, L.Papadavid, M.Bagot, O.Servitjie, E.Berti, E.Guenova, R.Stadler, C.Querfeld, A.M.Busschots, E.Hodak, A.Patsatsi, J.Sanches, M.Maule, J.Yoo, M.Kevin, P.Fava, S.Ribero, L.Zocchi, M.Rubatto, M.T.Fierro, U.Wehkamp, M.Marshalko, C.Mitteldorf, O.Akilov, P.Ortiz-Romero, T.Estrach, L.Vakeva, P.A.Enz, M.Wobser, M.Bayne, C.Jonak, M.Rubeta, A.Forbes, A.Bates, M.Battistella, R.Amel-Kashipaz, B.Vydianath, A.Combalia, E.Georgiou, E.Hauben, E.K.Hong, M.Jost, R.Knobler, I.Amitay-Laish, D.Miyashiro, J.Cury-Martins, X.Martinez, C.Muniesa, H.Prag-Naveh, V.Nikolaou, K.Quint, C.Ram-Wolff, K.Rieger, R.Stranzenbach, Á.Szepesi, S.Alberti-Violetti8, E.Felicity, L.Cerroni, W.Kempf, S.Whittaker, R.Willemze, Y.Kim, J.J.Scarisbrick, *TREATMENT OF EARLY-STAGE MYCOSIS FUNGOIDES: RESULTS FROM THE PROspective Cutaneous Lymphoma International Study (PROCLIPI study).* British Journal of Dermatology, 2020, In press
5. Scarisbrick, J.J., et al., *Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sezary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model.* J Clin Oncol, 2015. **33**(32): p. 3766-73.DOI: 10.1200/jco.2015.61.7142.
6. Gilson, D., et al., *British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018.* British Journal of Dermatology, 2019. **180**(3): p. 496-526.DOI: 10.1111/bjd.17240.
7. Bunn, P.A., Jr. and S.I. Lamberg, *Report of the Committee on Staging and Classification of Cutaneous T-Cell Lymphomas.* Cancer treatment reports, 1979. **63**(4): p. 725-728.
8. Agar, N.S., et al., *Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2010. **28**(31): p. 4730-4739.DOI: 10.1200/JCO.2009.27.7665 [doi].
9. Benton, E.C., et al., *A cutaneous lymphoma international prognostic index (CLIPi) for mycosis fungoides and Sezary syndrome.* European journal of cancer (Oxford, England : 1990), 2013. **49**(13): p. 2859-2868.DOI: 10.1016/j.ejca.2013.04.018 [doi].
10. Diamandidou, E., et al., *Prognostic factor analysis in mycosis fungoides/Sezary syndrome.* Journal of the American Academy of Dermatology, 1999. **40**(6 Pt 1): p. 914-924.DOI: S0190-9622(99)70079-4 [pii].
11. Diamandidou, E., et al., *Transformation of mycosis fungoides/Sezary syndrome: clinical characteristics and prognosis.* Blood, 1998. **92**(4): p. 1150-1159.
12. Scarisbrick, J.J., et al., *Prognostic significance of tumor burden in the blood of patients with erythrodermic primary cutaneous T-cell lymphoma.* Blood, 2001. **97**(3): p. 624-630.DOI: 10.1182/blood.v97.3.624 [doi].

13. Lindahl, L.M., et al., *Antibiotics inhibit tumor and disease activity in cutaneous T-cell lymphoma.* Blood, 2019. **134**(13): p. 1072-1083.DOI: 10.1182/blood.2018888107 [doi].
14. Booher, S., S.A. McCann, and M.C. Tawa, *Cutaneous T-Cell Lymphoma: Mycosis Fungoides/Sézary Syndrome, Part 2.* Journal of the Dermatology Nurses' Association, 2011. **3**(2).
15. Gutman, A.B., et al., *Soak and Smear: A Standard Technique Revisited.* Archives of Dermatology, 2005. **141**(12): p. 1556-1559.DOI: 10.1001/archderm.141.12.1556.
16. Querfeld C, R.S.T.K.T.M., *Cutaneous T-cell lymphoma (Mycosis fungoides and Sézary's syndrome)*, in *Conn's Current Therapy*, B.E.T. Rakel Re, Editor. 2006, Elsevier/Saunders: Philadelphia. p. 902-906.
17. Zackheim, H.S., M. Kashani-Sabet, and S. Amin, *Topical Corticosteroids for Mycosis Fungoides: Experience in 79 Patients.* Archives of Dermatology, 1998. **134**(8): p. 949-954.DOI: 10.1001/archderm.134.8.949.
18. Ling, T.C., et al., *British Association of Dermatologists and British Photodermatology Group guidelines for the safe and effective use of psoralen-ultraviolet A therapy 2015.* The British Journal of Dermatology, 2016. **174**(1): p. 24-55.DOI: 10.1111/bjd.14317.
19. Dogra, S. and R. Mahajan, *Phototherapy for mycosis fungoides.* Indian Journal of Dermatology, Venereology, and Leprology, 2015. **81**(2): p. 124.DOI: 10.4103/0378-6323.152169.
20. Querfeld, C., et al., *Long-term follow-up of patients with early-stage cutaneous T-cell lymphoma who achieved complete remission with psoralen plus UV-A monotherapy.* Archives of Dermatology, 2005. **141**(3): p. 305-311.DOI: 10.1001/archderm.141.3.305.
21. Roenigk, H.H., et al., *Photochemotherapy alone or combined with interferon alpha-2a in the treatment of cutaneous T-cell lymphoma.* The Journal of Investigative Dermatology, 1990. **95**(6 Suppl): p. 198S-205S.DOI: 10.1111/1523-1747.ep12875523.
22. Oğuz, O., B. Engin, and E.H. Aydemir, *The influence of psoralen + ultraviolet A treatment on the duration of remission and prognosis in mycosis fungoides.* Journal of the European Academy of Dermatology and Venereology : JEADV, 2003. **17**(4): p. 483-485.DOI: 10.1046/j.1468-3083.2003.00614_10.x.
23. Herrmann, J.J., et al., *Treatment of mycosis fungoides with photochemotherapy (PUVA): long-term follow-up.* Journal of the American Academy of Dermatology, 1995. **33**(2 Pt 1): p. 234-242.DOI: 10.1016/0190-9622(95)90241-4.
24. Gathers, R.C., et al., *Narrowband UVB phototherapy for early-stage mycosis fungoides.* Journal of the American Academy of Dermatology, 2002. **47**(2): p. 191-197.DOI: S0190962202000476 [pii].
25. Clark, C., et al., *Narrowband TL-01 phototherapy for patch-stage mycosis fungoides.* Archives of Dermatology, 2000. **136**(6): p. 748-752.DOI: boo02 [pii].
26. Ramsay, D.L., et al., *Ultraviolet-B phototherapy for early-stage cutaneous T-cell lymphoma.* Archives of Dermatology, 1992. **128**(7): p. 931-933.

27. Milstein, H.J., et al., *Home ultraviolet phototherapy of early mycosis fungoides: preliminary observations.* Journal of the American Academy of Dermatology, 1982. **6**(3): p. 355-362.DOI: S0190-9622(82)70029-5 [pii].
28. Ponte, P., V. Serrão, and M. Apetato, *Efficacy of narrowband UVB vs. PUVA in patients with early-stage mycosis fungoides.* Journal of the European Academy of Dermatology and Venereology: JEADV, 2010. **24**(6): p. 716-721.DOI: 10.1111/j.1468-3083.2009.03500.x.
29. Resnik, K.S. and E.C. Vonderheid, *Home UV phototherapy of early mycosis fungoides: long-term follow-up observations in thirty-one patients.* Journal of the American Academy of Dermatology, 1993. **29**(1): p. 73-77.DOI: 0190-9622(93)70155-M [pii].
30. Pavlotsky, F., et al., *UVB in the management of early stage mycosis fungoides.* Journal of the European Academy of Dermatology and Venereology : JEADV, 2006. **20**(5): p. 565-572.DOI: JDV1557 [pii].
31. Stern, R.S., *The risk of melanoma in association with long-term exposure to PUVA.* Journal of the American Academy of Dermatology, 2001. **44**(5): p. 755-761.DOI: 10.1067/mjd.2001.114576.
32. Stern, R.S., K.T. Nichols, and L.H. Väkevä, *Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). The PUVA Follow-Up Study.* The New England Journal of Medicine, 1997. **336**(15): p. 1041-1045.DOI: 10.1056/NEJM199704103361501.
33. Hüsken, A.C., et al., *Comparison of pegylated interferon α-2b plus psoralen PUVA versus standard interferon α-2a plus PUVA in patients with cutaneous T-cell lymphoma.* Journal of the European Academy of Dermatology and Venereology: JEADV, 2012. **26**(1): p. 71-78.DOI: 10.1111/j.1468-3083.2011.04011.x.
34. Stadler, R., et al., *Prospective randomized multicenter clinical trial on the use of interferon -2a plus acitretin versus interferon -2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II.* Blood, 1998. **92**(10): p. 3578-3581.
35. Kuzel, T.M., et al., *Effectiveness of interferon alfa-2a combined with phototherapy for mycosis fungoides and the Sézary syndrome.* Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 1995. **13**(1): p. 257-263.DOI: 10.1200/JCO.1995.13.1.257.
36. Neelis, K.J., et al., *Low-dose palliative radiotherapy for cutaneous B- and T-cell lymphomas.* International journal of radiation oncology, biology, physics, 2009. **74**(1): p. 154-158.DOI: 10.1016/j.ijrobp.2008.06.1918 [doi].
37. Cotter, G.W., et al., *Palliative radiation treatment of cutaneous mycosis fungoides--a dose response.* Int J Radiat Oncol Biol Phys, 1983. **9**(10): p. 1477-80.DOI: 10.1016/0360-3016(83)90321-8.
38. Esposito, L., et al., *Results of radiotherapy in minimal stage mycosis fungoides: a reappraisal after ten years.* G Ital Dermatol Venereol, 2018.DOI: 10.23736/s0392-0488.18.05914-x.

39. Jones, G.W., et al., *Prognosis with newly diagnosed mycosis fungoides after total skin electron radiation of 30 or 35 GY.* International journal of radiation oncology, biology, physics, 1994. **28**(4): p. 839-845.DOI: 0360-3016(94)90103-1 [pii].
40. Hoppe, R.T., Z. Fuks, and M.A. Bagshaw, *The rationale for curative radiotherapy in mycosis fungoides.* Int J Radiat Oncol Biol Phys, 1977. **2**(9-10): p. 843-51.DOI: 10.1016/0360-3016(77)90182-1.
41. Campbell, B.A., et al., *Lack of Durable Remission with Conventional-Dose Total Skin Electron Therapy for the Management of Sezary Syndrome and Multiply Relapsed Mycosis Fungoides.* Cancers (Basel), 2019. **11**(11).DOI: 10.3390/cancers11111758.
42. Specht, L., et al., *Modern radiation therapy for primary cutaneous lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group.* Int J Radiat Oncol Biol Phys, 2015. **92**(1): p. 32-9.DOI: 10.1016/j.ijrobp.2015.01.008.
43. Kamstrup, M.R., et al., *A prospective, open-label study of low-dose total skin electron beam therapy in mycosis fungoides.* International Journal of Radiation Oncology, Biology, Physics, 2008. **71**(4): p. 1204-1207.DOI: 10.1016/j.ijrobp.2007.11.039.
44. Harrison, C., et al., *Revisiting low-dose total skin electron beam therapy in mycosis fungoides.* International Journal of Radiation Oncology, Biology, Physics, 2011. **81**(4): p. 651.DOI: 10.1016/j.ijrobp.2011.01.023.
45. Specht, L., et al., *Modern radiation therapy for primary cutaneous lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group.* International Journal of Radiation Oncology, Biology, Physics, 2015. **92**(1): p. 32-39.DOI: 10.1016/j.ijrobp.2015.01.008.
46. Huen, A.O. and E.J. Kim, *The Role of Systemic Retinoids in the Treatment of Cutaneous T-Cell Lymphoma.* Dermatol Clin, 2015. **33**(4): p. 715-29.DOI: 10.1016/j.det.2015.05.007.
47. Vonderheid, E.C., et al., *Recombinant interferon alfa-2b in plaque-phase mycosis fungoides. Intralesional and low-dose intramuscular therapy.* Archives of Dermatology, 1987. **123**(6): p. 757-763.
48. Kohn, E.C., et al., *Phase II trial of intermittent high-dose recombinant interferon alfa-2a in mycosis fungoides and the Sézary syndrome.* Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 1990. **8**(1): p. 155-160.DOI: 10.1200/JCO.1990.8.1.155.
49. Olsen, E.A. and P.A. Bunn, *Interferon in the treatment of cutaneous T-cell lymphoma.* Hematology/Oncology Clinics of North America, 1995. **9**(5): p. 1089-1107.
50. Prince, H.M.P., et al., *Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial.* Lancet, The, 2017. **390**(10094): p. 555-566.DOI: 10.1016/S0140-6736(17)31266-7.

51. Morris, S., et al., *The Results of Low-Dose Total Skin Electron Beam Radiation Therapy (TSEB) in Patients With Mycosis Fungoides From the UK Cutaneous Lymphoma Group.* International Journal of Radiation Oncology, Biology, Physics, 2017. **99**(3): p. 627-633.DOI: 10.1016/j.ijrobp.2017.05.052.
52. Kamstrup, M.R., et al., *Low-dose total skin electron beam therapy as a debulking agent for cutaneous T-cell lymphoma: an open-label prospective phase II study.* The British Journal of Dermatology, 2012. **166**(2): p. 399-404.DOI: 10.1111/j.1365-2133.2011.10670.x.
53. Hoppe, R.T., et al., *Low-dose total skin electron beam therapy as an effective modality to reduce disease burden in patients with mycosis fungoides: results of a pooled analysis from 3 phase-II clinical trials.* J Am Acad Dermatol, 2015. **72**(2): p. 286-92.DOI: 10.1016/j.jaad.2014.10.014.
54. Olsen, E., et al., *Vorinostat (suberoylanilide hydroxamic acid, SAHA) is clinically active in advanced cutaneous T-cell lymphoma (CTCL): Results of a phase IIb trial.* Journal of Clinical Oncology, 2006. **24**(18_suppl): p. 7500-7500.DOI: 10.1200/jco.2006.24.18_suppl.7500.
55. Duvic, M., et al., *Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL).* Blood, 2007. **109**(1): p. 31-39.DOI: 10.1182/blood-2006-06-025999.
56. Kim, Y.H., et al., *Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial.* The Lancet.Oncology, 2018. **19**(9): p. 1192-1204.DOI: S1470-2045(18)30379-6 [pii].
57. Whittaker, S.J., et al., *Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma.* Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 2010. **28**(29): p. 4485-4491.DOI: 10.1200/JCO.2010.28.9066.
58. Duvic, M., et al., *Responses to romidepsin in patients with cutaneous T-cell lymphoma and prior treatment with systemic chemotherapy.* Leukemia & lymphoma, 2018. **59**(4): p. 880-887.DOI: 10.1080/10428194.2017.1361022 [doi].
59. Thursky, K.A., et al., *Spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab*.* British Journal of Haematology, 2006. **132**(1): p. 3-12.DOI: 10.1111/j.1365-2141.2005.05789.x.
60. Wu, P.A., et al., *A Meta-analysis of Patients Receiving Allogeneic or Autologous Hematopoietic Stem Cell Transplant in Mycosis Fungoides and Sézary Syndrome.* Biol Blood Marrow Transplant, 2009. **15**(8): p. 982-90.DOI: 10.1016/j.bbmt.2009.04.017.
61. Burt, R., et al., *Allogeneic hematopoietic stem cell transplantation for advanced mycosis fungoides: evidence of a graft-versus-tumor effect.* Bone Marrow Transplantation, 2000. **25**(1): p. 111-113.DOI: doi:10.1038/sj.bmt.1702099.

62. Sureda, A., et al., *Allogeneic hematopoietic stem cell transplantation for relapsed follicular lymphoma: A combined analysis on behalf of the Lymphoma Working Party of the EBMT and the Lymphoma Committee of the CIBMTR.* Cancer, 2018. **124**(8): p. 1733-1742.DOI: 10.1002/cncr.31264.
63. Duarte, R.F., et al., *Long-term outcome of allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sezary syndrome: a European society for blood and marrow transplantation lymphoma working party extended analysis*, in *J Clin Oncol*. 2014: United States. p. 3347-8.DOI: 10.1200/jco.2014.57.5597.
64. Lechowicz, M.J., et al., *ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR MYCOSIS FUNGOIDES AND SEZARY SYNDROME.* Bone Marrow Transplant, 2014. **49**(11): p. 1360-5.DOI: 10.1038/bmt.2014.161.
65. de Masson, A., et al., *Allogeneic stem cell transplantation for advanced cutaneous T-cell lymphomas: a study from the French Society of Bone Marrow Transplantation and French Study Group on Cutaneous Lymphomas.* Haematologica, 2014. **99**(3): p. 527-34.DOI: 10.3324/haematol.2013.098145.
66. Cudillo, L., et al., *Allogeneic hematopoietic stem cell transplantation in Primary Cutaneous T Cell Lymphoma.* Ann Hematol, 2018. **97**(6): p. 1041-1048.DOI: 10.1007/s00277-018-3275-z.
67. Hosing, C., et al., *Allogeneic stem-cell transplantation in patients with cutaneous lymphoma: updated results from a single institution.* Ann Oncol, 2015. **26**(12): p. 2490-5.DOI: 10.1093/annonc/mdv473.
68. Ahlawat, S.e.a., *A multi-centre retrospective analysis of outcomes following allogeneic stem-cell transplant in patients with cutaneous T-cell lymphoma.* . 2019: T-cell Lymphoma Forum, La Jolla
69. Gao, C., et al., *Prolonged survival with the early use of a novel extracorporeal photopheresis regimen in patients with Sezary syndrome.* Blood, 2019. **134**(16): p. 1346-1350.DOI: 10.1182/blood.2019000765 [doi].
70. Wilson, L.D., et al., *Experience with total skin electron beam therapy in combination with extracorporeal photopheresis in the management of patients with erythrodermic (T4) mycosis fungoides.* J Am Acad Dermatol, 2000. **43**(1 Pt 1): p. 54-60.DOI: 10.1067/mjd.2000.105510.
71. Duvic, M., et al., *Total skin electron beam and non-myeloablative allogeneic hematopoietic stem-cell transplantation in advanced mycosis fungoides and Sezary syndrome.* J Clin Oncol, 2010. **28**(14): p. 2365-72.DOI: 10.1200/jco.2009.25.8301.
72. Querfeld, C., et al., *Results of an open-label multicenter phase 2 trial of lenalidomide monotherapy in refractory mycosis fungoides and Sezary syndrome.* Blood, 2014. **123**(8): p. 1159-1166.DOI: 10.1182/blood-2013-09-525915 [doi].
73. Khodadoust, M.S., et al., *Pembrolizumab in Relapsed and Refractory Mycosis Fungoides and Sezary Syndrome: A Multicenter Phase II Study.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2020. **38**(1): p. 20-28.DOI: 10.1200/JCO.19.01056 [doi].