Pan Birmingham NHS
Cancer Network

Guideline for the Management of Patients with Cutaneous T-Cell Lymphoma

Version History

Version	Date	Summary of Change/Process
0.1	13.09.07	National guideline adopted by Skin Network Site Specific Group
1.0	04.09.08	Endorsed by Network Governance Committee following confirmation with Skin Network Site Specific Group Chair that this is the current version from the Association
1.1	30.06.11	Skin Network Site Specific Group agreed to continue adoption of National guidance.
2.0	11.07.11	Reviewed and endorsed by Guidelines Sub Group

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Date for Review	**July 2014**

1. Guideline Background

Burton Hospitals NHS Trust, Sandwell and West Birmingham Hospitals NHS Trust, Walsall Healthcare NHS Trust and Worcestershire Acute Hospitals NHS Trust have a local specialist multi disciplinary team for skin cancer. The specialist multi disciplinary teams are located at Heart of England NHS Foundation Trust and University Hospitals Birmingham NHS Foundation Trust.

2. Guideline Statement

The Joint British Association of Dermatologists and UK Cutaneous Lymphoma Group Guidelines for the Management of Primary Cutaneous T-Cell Lymphoma have been adopted by the Pan Birmingham Cancer Network to guide the treatment for patients with cutaneous T cell lymphoma (see appendix 1 attached).

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ENDORSED BY GOVERNANCE COMMITTEE

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GUIDELINES

Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas

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These guidelines were commissioned by the British Association of Dermatologists guidelines and therapeutics subcommittee. Members of the committee are N.H.Cox (Chairman), A.S.Highet, D.Mehta, R.H.Meyrick Thomas, A.D.Ormerod, J.K.Schofield, C.H.Smith and J.C.Sterling. Members of the U.K. Cutaneous Lymphoma Group who have contributed include C.Benton, R.Cowan, C.Deardon, B.Hancock, H.Lucraft and D.Slater.

Disclaimer These guidelines have been prepared for dermatologists on behalf of the British Association of Dermatologists and the U.K. Cutaneous Lymphoma Group (UKCLG) and reflect the best data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from the guidelines in special circumstances. Just as adherence to guidelines may not constitute defence against a claim of negligence, so deviation from them should not be necessarily deemed negligent.

Summary These guidelines for the management of cutaneous T-cell lymphoma have been prepared for dermatologists on behalf of the British Association of Dermatologists and the U.K. Cutaneous Lymphoma Group. They present evidence-based guidance for treatment, with identification of the strength of evidence available at the time of preparation of the guidelines, and a brief overview of epidemiological aspects, diagnosis and investigation.

Epidemiology

The incidence of cutaneous lymphomas is 0·4 per 100 000 per year but, because most are low-grade malignancies with long survival, the overall prevalence is much higher. Approximately two-thirds of primary cutaneous lymphomas are of T-cell origin (cutaneous T-cell lymphoma, CTCL), of which the majority are mycosis fungoides. Studies suggest that the incidence is rising but this may reflect improved diagnosis and better registration. The disease is commoner in males and, in the U.S.A., in the black population. The European Organization for Research and Treatment of Cancer (EORTC) cutaneous lymphoma classification (Appendix A) defines several well characterized clinicopathological entities for primary CTCL and forms a useful basis for a rational approach to therapy.[1] Most of the CTCL entities defined by the EORTC have been recognized in the recent WHO classification for lymphoma,[2] shown in Appendix A. The staging systems are shown in Appendix B.

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Conflicts of interest by authors: Dr Sean J.Whittaker has previously acted as an expert witness for Ligand Pharmaceuticals with regard to European licensing applications for bexarotene gel and denileukin diftitox.

Initial assessment

This article is restricted to the management of primary CTCL, and specifically of mycosis fungoides and Sézary syndrome. Two sections devoted to primary cutaneous CD30+ lymphoproliferative disorders and rare CTCL variants are found towards the end of the article. It is recommended that all patients, possibly with the exception of those with early stages of mycosis fungoides (IA) or with lymphomatoid papulosis, should be reviewed by a multidisciplinary team (MDT) which should include a dermatologist, a clinical or medical (haemato)oncologist, and a dermatopathologist or pathologist with considerable experience of the diagnosis and management of primary CTCL. In addition, a central review of all pathology would be desirable, consistent with current recommendations from the Royal College of Pathologists for specialized pathology services. Subsequent management should ideally be shared between the cancer centre and the local referring physician in a cancer unit. The MDT should ideally be supported by an accredited laboratory for immunophenotypic and molecular diagnostic studies in lymphoma.

All patients should have adequate diagnostic biopsies for histology, immunophenotypic and preferably molecular studies. This is advised even for stage IA disease as studies have shown that patients with a detectable T-cell clone have a shorter duration of response and higher rate of failure to respond. These findings should be interpreted with the clinical features in order to make a specific diagnosis based on the WHO classification for primary CTCL. This is critical because treatment and prognosis can vary widely depending on the diagnostic category. Occasionally, multiple skin biopsies are required to make a diagnosis and often the opinion of other dermatopathologists experienced in cutaneous lymphoma is required. The patient should be examined fully and any bulky palpable peripheral nodes should be biopsied, preferably by excision rather than by core or fine needle biopsy. Staging computed tomographic (CT) scans of the chest, abdomen and pelvis are indicated in all those patients with non-mycosis fungoides CTCL variants or with stage IIA/B/III/IV mycosis fungoides, but not in those with stage IA/IB disease or lymphomatoid papulosis. Bone marrow aspirate or trephine biopsies are indicated in all patients with CTCL variants (except lymphomatoid papulosis), and should be considered in stage IIB/III/IV mycosis fungoides and also in patients with peripheral blood involvement (as indicated by the presence of Sézary cell counts representing $> 5\%$ of the total lymphocyte count). Peripheral blood samples should be taken for routine haematology, biochemistry, serum lactate dehydrogenase (LDH), Sézary cells, lymphocyte subsets, CD4/CD8 ratio, human T-cell lymphotropic virus (HTLV)-I serology and T-cell receptor (TCR) gene analysis of peripheral blood mononuclear cells. These tests are necessary to distinguish patients with HTLV-I-associated adult T-cell leukaemia/lymphoma (ATLL) and other T-cell leukaemias such as T-prolymphocytic leukaemia (T-PLL), and also to identify those with T-cell clones in peripheral blood as a marker of tumour burden and as a prognostic indicator. On the basis of these findings a specific clinicopathological diagnosis should be established and all patients should be accurately staged, providing prognostic data (Table 1).[3–8]

Recommendations: initial assessment

- Repeated skin biopsies (ellipse rather than punch) are often required to confirm a diagnosis of CTCL
- Histology, immunophenotypic and preferably TCR gene analysis should be performed on all tissue samples (ideally molecular studies require fresh tissue)
- All patients (with the possible exception of early stage mycosis fungoides (stage IA) and lymphomatoid papulosis) should ideally be reviewed by an appropriate MDT for confirmation of the diagnosis and to establish a management strategy
- Initial staging CT scans are required in all patients with the exception of those with early stages of mycosis fungoides (stage IA/IB) and lymphomatoid papulosis
- At diagnosis peripheral blood samples should be analysed for total white cell, lymphocyte and Sézary cell counts, serum LDH, liver and renal function, lymphocyte subsets, CD4/CD8 ratios, HTLV-I serology and, preferably, TCR gene analysis
- Bone marrow aspirate or trephine biopsies are required for CTCL variants (with the exception of lymphomatoid papulosis) and may also be appropriate for those with late stages of mycosis fungoides (stage IIB or above). *Grade A/level III* (*Appendix C*)

Recommendations: histology

- The presence or absence of epidermotropism should be documented
- The depth of the infiltrate should be noted

Table 1. Prognosis in cutaneous T-cell lymphoma

Stage	IA	IB	IIA	IIB	III	IVA	IVB
OS at 5 y	96–100%	73–86%	49–73%	40–65%	40–57%	15–40%	0–15%
OS at 10 y	84–100%	58–67%	45–49%	20–39%	20–40%	5–20%	0–5%
DSS at 5 y	100%	96% (81%[a])	68%	80%		40%	0%
DSS at 10 y	97–98%	83% (36%[a])	68%	42%		20%	0%
Median survival	Not reached at 32 y	12·1–12·8 y	10·0 y	2·9 y	3·6–4·6 y	13 mo	13 mo
Disease progression at 5 y	4%	21%	65%	32%		70%	100%
Disease progression at 10 y	10%	39%	65%	60%		70%	100%
Overall disease progression	9%	20%	34%				
FFR at 5 y	50%	36%	9%				
FFR at 10 y		31%	3%				

OS, overall survival; DSS, disease-specific survival; FFR, freedom from relapse; y, years; mo, months. Based on data.[3–8] [a]Indicates DSS at 5 y and 10 y for stage IB patients with folliculotropic mycosis fungoides.[65]

- The morphology or cytology of the atypical cells and presence of large cell transformation, folliculotropism, syringotropism, granuloma formation, angiocentricity and subcutaneous infiltration should be mentioned
- Immunophenotypic studies should be performed on paraffin-embedded sections and include the T-cell markers CD2, CD3, CD4, CD8, B-cell marker CD20 and the activation marker CD30. Additional markers such as p53 may have prognostic significance in mycosis fungoides. Markers of cytotoxic function such as TIA-I, the monocyte/macrophage marker CD68 and natural killer (NK) cell marker CD56 may be useful for specific CTCL variants
- Ideally all pathology results should be reviewed by a central panel (usually within cancer centres) as recommended for specialized pathology services
- The histology, after correlation with the clinical features, should be classified according to an integration of the WHO and EORTC classification. (*Grade A/level III)*

Mycosis fungoides/Sézary syndrome

Therapeutic overview. There has been one pivotal randomized controlled trial in patients with CTCL at diagnosis and the majority of these patients had mycosis fungoides.[9] This study compared palliative therapy, consisting of topical mechlorethamine, superficial radiotherapy and phototherapy with combined total skin electron beam (TSEB) therapy and multiagent chemotherapy consisting of cyclophosphamide, adriamycin, vincristine and etoposide (CAVE). The complete response rate was higher in the chemotherapy group (38% compared with 18%) but morbidity was greater and, critically, there was no significant difference in disease-free or overall survival between the two groups after a median follow-up of 75 months.[9] This study provides the rationale for the management of mycosis fungoides which is based on a skin-directed palliative approach that varies according to the stage of the disease. There have been a large number of uncontrolled studies in CTCL with response data but virtually no other controlled studies with data on disease-free and overall survival.[10] This partly reflects the prolonged survival of patients with early stage disease.

Prognosis. Recent findings suggest that a patient's life expectancy is not adversely affected in stage IA disease.[3–5] Patients with stage IB/IIA disease have a 73–86% or 49–73% overall 5-year survival, respectively, while patients with stage IIB disease have a 40–65% 5-year survival.[3–5] The 5-year survival of patients with erythrodermic stage III disease is 45–57%, 15–40% for those with stage IVA and 0–15% for IVB disease.[3,4,7,8] Recent studies also suggest that stage A/B patients with thick plaques may have a worse prognosis but this depends on a histological assessment of plaque thickness and there are concerns that this might not be reproducible. The presence of a peripheral blood T-cell clone may indicate which patients with early stage disease are likely to develop disease progression.[11] Sézary syndrome patients by definition are staged as T4 N1–3 M0 B1 and have a poor prognosis with an overall median survival of 32 months from diagnosis.[1] Recent studies

of erythrodermic CTCL have shown that the presence of peripheral nodal disease is the most important prognostic factor in a multivariate analysis although the degree of haematological involvement was also very close to significance.[12] Unfortunately most studies of erythrodermic CTCL have not staged erythrodermic patients adequately and therefore accurate comparisons of different therapies are difficult.

There are a number of clinical variants of mycosis fungoides including localized disease such as pagetoid reticulosis (Woringer Kolopp), folliculotropic mycosis fungoides (follicular mucinosis), poikilodermatous mycosis fungoides, hypopigmented mycosis fungoides and granulomatous slack skin.[1] Although there have been no specific therapeutic trials in these variants, these clinical variants appear to have a good prognosis and are often responsive to skin-directed therapies such as radiotherapy. The exception is folliculotropic mycosis fungoides which may have a worse prognosis.

Recommendations: prognosis

- Prognosis in mycosis fungoides (and clinical variants) is related to age at presentation (worse if > 60 years), to the stage of the disease and possibly to the presence of a peripheral blood T-cell clone; some mycosis fungoides clinical variants may have a better prognosis
- In Sézary syndrome the median survival is 32 months from diagnosis
- Primary cutaneous CD30+ lymphoproliferative disorders without peripheral nodal disease have an excellent prognosis (range 96–100% 5-year survival)
- The prognosis of other types of CTCL is generally poor with the frequent development of systemic disease. (*Grade A/level IIii*)

Therapy

Topical therapy

For patients with limited early stage mycosis fungoides life expectancy may not be adversely affected; it is acceptable simply to use emollients with or without moderate topical steroids. Potent topical corticosteroids can produce a clinical response although this is usually short-lived.[13]

Topical mechlorethamine (nitrogen mustard) 0·01% or 0·02%, either as an aqueous solution (in normal saline) or in an ointment base (emulsifying ointment), is effective for superficial disease with response rates of 51–80% for stage IA, 26–68% for IB and 61% for IIA disease.[14–16] The aqueous solution is relatively unstable, and the ointment base, which is more irritant than the aqueous solution, can cause irritant or allergic dermatitis in sensitized individuals (35–58%), but its efficacy is similar. This product must not be used in pregnancy but other concerns about safety have not been realized. There is no consensus as to whether mechlorethamine should be applied to individual lesions or to the whole skin, daily or twice weekly, or about the duration of topical therapy after a clinical remission has been produced, but responses can be sustained for prolonged periods. (*Grade A/level IIii*)

Topical carmustine (BCNU) is an alternative topical chemotherapeutic agent in mycosis fungoides with similar efficacy to mechlorethamine as indicated by response rates of 86% in stage IA, 47% in stage IB and 55% in stage IIA patients.[17] Alternate day or daily treatment with 10 mg of BCNU in 60 mL of dilute alcohol (95%) or 20–40% BCNU ointment can be used. Hypersensitivity reactions occur less often (5–10%) than with mechlorethamine. All patients treated topically with BCNU should have regular monitoring of their full blood count; treatment is normally given for only a limited period, depending on the extent of the treated area (2–4 weeks for extensive areas), to avoid myelosuppression; maintenance therapy is contraindicated. (*Grade A/level IIii*)

Recently a novel retinoid, 1% targretin (bexarotene) gel, has been approved by the Federal Drug Administration (FDA) for topical therapy in stage I mycosis fungoides in patients who are resistant or intolerant of other topical therapies.[18] In open uncontrolled studies response rates of 63% with 21% complete response rates have been reported in 67 patients with early stage (IA–IIA) disease. Median time to and duration of response were 20 and 99 weeks, respectively.[18] This product is currently not licensed in Europe. (*Grade B/level IIii*)

There has been only one randomized placebo controlled trial of topical peldesine cream (BCX-34, an inhibitor of the purine nucleoside phosphorylase enzyme) in mycosis fungoides, which showed no benefit compared with vehicle, with complete responses of 28% and 24%, respectively, emphasizing the difficulties in interpretation of uncontrolled studies of topical therapy in early stages of mycosis fungoides.[19] (*Grade E/level I*)

Phototherapy

The clinical benefit of photochemotherapy [psoralen + ultraviolet A (PUVA)] was noted over 20 years ago and response rates of 79–88% in stage IA and

52–59% in stage IB disease have been reported.[20,21] Flexural sites ('sanctuary sites') often fail to respond completely and the duration of response varies. There is no significant response in tumour (IIB) stage disease. Maintenance therapy is rarely effective at preventing relapse[22] and therefore should be avoided if possible so as to limit the total cumulative dose as patients will often require repeated courses over many years. One study has shown that 56% of stage IA and 39% of stage IB complete PUVA responders had no recurrence of disease after 44 months, follow-up without maintenance therapy.[22] PUVA is an ideal therapy for patients with stage IB/IIA disease who are intolerant of or fail to respond to topical therapies such as mechlorethamine although both therapies can be complementary for some patients. Treatment schedules have varied in reported studies of PUVA in CTCL with twice to four times weekly and different protocols for incremental dosage but usually two to three times weekly treatment is acceptable until disease clearance or best partial response. Many patients will inevitably have a high total cumulative UVA dose and the risks of nonmelanoma skin cancer are consequently increased for these patients. Therefore efforts should be made to restrict the total PUVA dose to less than 200 treatment sessions or a total cumulative dose of 1200 J cm^{-2}. In some circumstances patients may receive a greater total dose, if clinically justified and with the consent of the patient. PUVA remains one of the most effective therapies for patients with early stage disease but surprisingly there are no data to establish if PUVA can improve overall survival. PUVA therapy is rarely tolerated in erythrodermic disease but some patients will respond repeatedly. (*Grade A/level IIii*)

Broadband and narrowband UVB and high-dose UVA1 phototherapy have also been used with benefit in mycosis fungoides.[23–25] There have been no adequate comparative studies of different phototherapy modalities or regimens in CTCL. (*Grade B/level III*)

Radiotherapy

Mycosis fungoides and other CTCL variants are very radiosensitive malignancies; individual thick plaques, eroded plaques or tumours can be treated successfully with low-dose superficial orthovoltage radiotherapy, often administered in several fractions (e.g. two or three fractions of 400 cGy at 80–120 kV). Large tumours may be treated by electrons, the choice of energy being dependent on tumour size and thickness. Radiotherapy is often used with other therapeutic modalities such as PUVA; closely adjacent and overlapping fields can often be retreated because of the low doses used.[26] (*Grade A/level IIii*)

Whole body TSEB therapy has been evaluated extensively in CTCL although it is not widely available. Different field arrangements have been used in an attempt to treat the whole skin uniformly to a depth of 1 cm with various total doses administered and with additional radiotherapy to shielded areas. A systematic review of open uncontrolled and mostly retrospective studies of TSEB as monotherapy in 952 patients with CTCL has established that responses are stage-dependent with complete responses of 96% in stage IA, IB and IIA disease but disease relapse rates are very high, indicating that this approach is not curative even in early stage disease.[27] In stage IIB disease complete responses are less common (36%) but erythrodermic (stage III) disease shows complete responses of 60%. Greater skin surface dose (32–36 Gy) and higher energy (4–6 MeV electrons) are associated with a higher rate of complete response and 5-year relapse-free survivals of 10–23% were noted.[27] A retrospective study of erythrodermic disease has also shown 60% complete responses with 26% progression-free at 5 years.[28] In this study the overall median survival was 3·4 years with a median dose of 32 Gy given as five weekly fractions over 6–9 weeks. Patients with stage III disease did best compared with those with significant nodal or haematological (IVA/IVB) disease. The duration of response was also longer for those who received more than 20 Gy using 4–9 MeV.[28]

A comparative study of TSEB vs. topical mechlorethamine in early stage mycosis fungoides showed similar response rates and duration of response suggesting that TSEB therapy should be reserved for those who fail to respond to first- and second-line therapies.[29] Adverse effects of TSEB include temporary alopecia, telangiectasia and skin malignancies, and the treatment is only available in a limited number of centres.

Although TSEB is usually only given once in a lifetime, several reports have documented patients who have received two or three courses; however, the total doses tolerated and the duration of response have been lower with subsequent courses.[30,31] Consensus EORTC recommendations for the clinical use of TSEB have been published with technical modifications to optimize the efficacy of therapy in CTCL.[32] (*Grade A/level IIii*)

Immunotherapy

Different forms of immunotherapy have been evaluated in CTCL with the intention of enhancing antitumour host immune responses by promoting the generation of cytotoxic T cells and Th1 cytokine responses. Studies of α-interferon have shown overall response rates of 45–74% with complete responses of 10–27%.[33–35] Various dosage schedules have been employed (3 MU × 3 week^{-1} to 36 MU day^{-1}) and it appears that response rates are higher for larger doses (overall responses of 78% vs. 37% for the lower dose schedule).[34] Overall response rates are also higher in early (IB/IIA 88%) compared with late (III/IV 63%) stages of disease.[35] (*Grade A/level IIi*)

Combined α-interferon and retinoids produce similar response rates to interferon alone and are not recommended.[36] (*Grade D/level IIi*)

Studies comparing PUVA and α-interferon with α-interferon and acitretin in early-stage disease have shown complete response rates of 70% and 38%, respectively, but there are no data on duration of response.[37] Uncontrolled studies of combined PUVA and α-interferon (maximum tolerated dose 12 MU m^{-2} × 3 week^{-1}) in mycosis fungoides and Sézary syndrome have shown overall response rates of 100% with 62% complete response rates.[38] This combination may also be useful in patients with resistant early-stage disease such as those with thick plaques and folliculotropic disease. (*Grade A/level IIii*)

A recently completed randomized study comparing PUVA with PUVA and α-interferon in early-stage mycosis fungoides suggests that the response rates are similar but the cumulative dose is lower and the duration of response is more prolonged for the combined regimen (EORTC Annual Clinical Meeting, Helsinki June 2003). At present there are few data about the effect on disease-free and overall survival.

Other small pilot studies have shown that both interleukin (IL)-12 and γ-interferon can produce clinical responses in CTCL but their therapeutic value remains to be established.[39,40] (*Grade C/level III*)

Ciclosporin has been used in CTCL, particularly in erythrodermic variants to relieve severe pruritus, but there is some evidence that treatment may actually cause rapid disease progression and its use in CTCL is not recommended.[41] (*Grade D/level III*)

Chemotherapy

Mycosis fungoides and Sézary syndrome are relatively chemoresistant and responses are usually short-lived, as illustrated by the controlled study by Kaye *et al.*[9] This may reflect the low proliferative rate of tumour cells and a high prevalence of inactivating p53 mutations which produce a relative resistance to tumour cell apoptosis. A systematic review of published data on different regimens has shown a complete response rate of 33% in 526 patients treated with single agent chemotherapy with a median duration of 3–22 months.[42] Combination chemotherapy in 331 patients produced complete response rates of 38% with a median duration of 5–41 months.[42] CTCL patients are prone to infection and septicaemia is a common preterminal event.

Chemotherapy should not be used in patients with early stage IA, IB or IIA disease. (*Grade E/level I*) However, treatment of stage IIB and IVA disease remains problematic. Individual tumours and effaced peripheral lymph nodes will respond to superficial radiotherapy and additional chemotherapy should be considered in patients with a good performance status [Eastern Cooperative Oncology Group (ECOG), 0–2, where 0 is 'fully active' and 4 is 'completely disabled']. However, responses are likely to be short-lived, and patients should be entered into ongoing clinical trials. Single agent chemotherapy which has been shown to produce a clinical response in stage IIB–IVB disease includes oral chlorambucil (4–6 cycles of 0·15–0·2 mg kg^{-1} day^{-1} for 2–4 weeks), methotrexate and etoposide, and the intravenous use of the purine analogues 2-deoxycoformycin, 2-chlorodeoxyadenosine and fludarabine.[42] Open studies of 2-deoxycoformycin in mycosis fungoides and Sézary syndrome have reported response rates of 35–71% with complete response rates of 10–33%.[43,44] Methotrexate has been reported to produce a complete response rate of 41% in 29 patients with erythrodermic (stage III/T4) disease with a median survival of 8·4 years given as single weekly doses over a wide dose range of 5–125 mg, but this study was uncontrolled and it is unclear if the patients included represented an usually good prognostic group.[45] Recently, liposomal doxorubicin and gemcitabine have been used in CTCL[46,47] and EORTC phase II trials are due to start shortly. All patients with a good performance status (ECOG 0–2) and advanced stages of mycosis fungoides should if possible be entered into randomized controlled studies. (*Grade B/level IIii*)

Recent pilot studies assessing the use of TSEB combined with high-dose conditioning chemotherapy before autologous stem cell transplantation in patients with stage IIB–IVA disease have shown good clinical responses,[48] but there are no data available at present

to indicate if this approach affects disease-free or overall survival. Patients with a poor prognosis and good performance status should be selected for existing clinical trials. Allogeneic stem cell or bone marrow transplantation has only been used in a few patients with encouraging results[49,50] but the associated mortality suggests that this approach is difficult to justify. However, a graft-versus-lymphoma effect may be therapeutically important and the future assessment of nonmyeloablative mini-allografts in CTCL would be appropriate. (*Grade C/level III*)

Monoclonal antibody therapy

A humanized chimeric anti-CD4 monoclonal antibody has been used to treat eight patients with CTCL; seven patients showed a clinical response but this was of short duration.[51] (*Grade C/level III*) A radiolabelled anti-CD5 antibody has also been used in mycosis fungoides with some objective results[52] and alemtuzumab (CAMPATH—anti-CD52) has also been administered to CTCL patients (stage III) with demonstrable but short-lived clinical responses.[53,54] At present these approaches are not considered standard treatment and remain potential options for future phase I/II studies. A current phase II study is assessing the therapeutic benefit of a fully humanized anti-CD4 antibody in both early and late stages of mycosis fungoides. (*Grade C/level III*)

Recently a novel antibody approach has been used in CTCL. Denileukin diftitox, a DAB_{389}–IL-2 fusion toxin (Onzar in Europe/Ontak in the U.S.A.) has completed phase I/II studies and has received provisional FDA approval for the treatment of resistant or recurrent CTCL, but this therapy has not yet received a license in Europe for late stages of mycosis fungoides or Sézary syndrome. Denileukin diftitox is a recombinant fusion protein consisting of peptide sequences for the enzymatically active domain (389) of diphtheria toxin and the membrane translocation domain of IL-2 and can inhibit protein synthesis in tumour cells that express high levels of the IL-2 receptor, thereby resulting in cell death. Phase III studies of 71 heavily pretreated patients with stage IB–IVA mycosis fungoides, and more than 20% CD25+ lymphocytes, showed an overall response rate (defined as lasting at least 6 months) of 30% including 10% with complete response.[55] The median duration of response was 6·9 months (range 2·7–46·1 months). The optimally tolerated dose (18 μg kg^{-1} day^{-1}) is given intravenously for 5 days and repeated every 21 days for four to eight cycles. Adverse effects include fever, chills, myalgia, nausea and vomiting, and a mild increase in transaminase levels. Acute hypersensitivity reactions occurred in 60%, invariably within 24 h and during the initial infusion. A vascular leak syndrome characterized by hypotension, hypoalbuminaemia and oedema was defined retrospectively within the first 14 days of a given dose in 25% of patients. Myelosuppression is rare. Five per cent of adverse effects are severe or life threatening. (*Grade A/level IIii.*) The clinical relevance of antibody responses to denileukin diftitox is unclear. The duration of clinical response has not yet been established and current studies are comparing different doses of denileukin diftitox and are also assessing the use of this therapy in CD25-negative tumours. This therapy is not likely to be appropriate for early-stage disease but may be useful in advanced disease. Patients should be treated with denileukin diftitox in the context of appropriate clinical trials.

Novel retinoids

Phase II and III studies of a novel synthetic retinoid in CTCL have recently been published.[56,57] Bexarotene (Targretin) is the only retinoid that selectively binds and activates the retinoid X receptor and has recently been approved in Europe for the treatment of advanced stages (IIB–IVB) of mycosis fungoides. Bexarotene has been shown to promote apoptosis and inhibit cell proliferation. It is relatively selective and therefore should have little effect on the retinoid A receptor (RAR) receptor involved in cell differentiation. In phase II and III studies of 152 patients with CTCL, response rates from 20% to 67% have been reported.[56,57] The most effective tolerated oral dose is 300 mg m^{-2} day^{-1} although responses improve with higher doses. Side-effects are transient and generally mild but most patients require treatment for hyperlipidaemia and central (hypothalamic) hypothyroidism while on therapy. At doses of 300 mg m^{-2} day^{-1} in early stage disease (IA/IB/IIA) response rates of 54% have been noted[56] whereas patients with advanced mycosis fungoides (stage IIB–IVB) have shown response rates of 45% with a notable reduction in pruritus in stage III disease.[57] (*Grade A/level IIii*)

EORTC studies due to start enrolment shortly include a phase III randomized study comparing PUVA alone with combined PUVA and oral bexarotene in stage IB and IIA disease. Future studies should also clarify the role of oral bexarotene in later stages of disease and

specifically in erythrodermic patients. At the present time oral bexarotene can only be prescribed for early stages of mycosis fungoides in the context of clinical trials.

Extracorporeal photopheresis

Extracorporeal photopheresis (ECP) is licensed by the FDA for the treatment of CTCL; there are no randomized studies to clarify whether ECP has any effect on overall survival. The original open study of ECP in 29 erythrodermic CTCL patients reported a response rate of 73% but response rates in patients with earlier stages of mycosis fungoides were much lower (38%).[58] Subsequently a median survival of 62 months was reported in the original cohort of 29 erythrodermic patients, which compares favourably with historical controls (30 months).[59] A study of 33 patients with Sézary syndrome treated with ECP reported a median survival of 39 months, which was similar to historical controls from the same institution.[60] A systematic review of response rates in erythrodermic disease (stage III/IVA) with ECP has shown overall responses of 35–71%, with complete responses of 14–26%.[61] Other studies are more difficult to interpret because they have involved small numbers, patients with earlier stages of disease and in most studies many of the patients have been on other concurrent therapies. (*Grade A/level IIii*)

Randomized controlled trials of ECP are required to assess its effect on disease-free and overall survival. There have been claims that the CD8 count is critical in predicting whether patients will respond to ECP,[59] although others have provided evidence that the total baseline Sézary count is the only predictor of response.[62]

Recommendations in mycosis fungoides and Sézary syndrome (Table 2)

- Skin-directed therapy (topical therapy, superficial radiotherapy and phototherapy) is appropriate treatment for patients with early stages of mycosis fungoides (stages IA–IIA) with the choice of therapy dependent on the extent of cutaneous disease and plaque thickness (*Grade A/level I*)
- Combined PUVA and α-interferon therapy can be effective for patients with resistant early-stage disease (stage IB–IIA) (*Grade A/level IIi*)
- Patients with later stages of mycosis fungoides (stage IIB or higher) will require some form of systemic therapy (*Grade A/level IIii*)
- CTCL is a very radiosensitive malignancy and several fractions (2–3) of low energy (80–120 kV) superficial radiotherapy are appropriate for many patients (*Grade A/level IIii*)
- Chemotherapy regimens in advanced stages of mycosis fungoides generally achieve complete responses in the region of 30% but these are short-lived (*Grade B/level IIii*)
- Erythrodermic CTCL patients should be considered for immunotherapy and ECP as responses to chemotherapy are generally poor (*Grade A/level IIii*)
- TSEB therapy is an effective treatment for stage IB and stage III mycosis fungoides but is not sufficient alone for stage IIB disease or those with significant haematological involvement (*Grade A/level IIi*)
- New agents such as bexarotene and denileukin diftitox offer important therapeutic alternatives which are currently being evaluated (*Grade A/level IIii*)
- In treatment-resistant cases of late stage disease palliative radiotherapy and/or chemotherapy may produce a significant short-term benefit but the patient's quality of life should always be given priority (*Grade B Level III*)
- All patients and especially those with late stages of disease (> IIA) should be considered for entry into well designed randomized controlled clinical trials.

Primary cutaneous CD30+ T-cell lymphomas

The primary cutaneous CD30+ T-cell lymphomas represent a spectrum of disease in which lymphomatoid papulosis represents an indolent form characterized by recurrent crops of self-healing papules and nodules which may become necrotic and usually resolve to leave varioliform scars. Histologically, lymphomatoid papulosis shows a wedge-shaped polymorphic infiltrate consisting of atypical mononuclear cells with cerebriform, anaplastic (CD30+) and pleomorphic cytology. In contrast larger tumours which do not resolve spontaneously and which histologically show a monomorphic infiltrate of large anaplastic CD30+ mononuclear cells (> 80% of dermal infiltrate) represent primary cutaneous anaplastic large cell lymphomas. Both conditions have an excellent prognosis with 100% and 96% 5-year survival for lymphomatoid papulosis and primary large cell anaplastic lymphomas, respectively, and therefore skin-directed therapy is indicated.[63] Lymphomatoid papulosis is radiosensitive and both PUVA therapy and low-dose oral methotrexate are effective at preventing recurrent lesions.[63,64] (*Grade*

Table 2. Treatment of mycosis fungoides/Sézary syndrome

Stage	First line	Second line	Experimental	Not suitable
IA	SDT or no therapy	SDT or no therapy	Bexarotene gel	Chemotherapy
IB	SDT	α-interferon + PUVA, TSEB	Denileukin diftitox, bexarotene	Chemotherapy
IIA	SDT	α-interferon + PUVA, TSEB	Denileukin diftitox, bexarotene	Chemotherapy
IIB	Radiotherapy or TSEB, chemotherapy	α-interferon, denileukin diftitox, bexarotene	Autologous PBSCT mini-allograft	Cyclosporin
III	PUVA ± α-interferon, ECP ± α-interferon, methotrexate	TSEB, bexarotene, denileukin diftitox,* chemotherapy, alemtuzumab	Autologous PBSCT, mini-allograft	Cyclosporin
IVA	Radiotherapy or TSEB, chemotherapy	α-interferon, denileukin diftitox,* alemtuzumab bexarotene	Autologous PBSCT, mini-allograft	Cyclosporin
IVB	Radiotherapy, chemotherapy	Palliative therapy	Mini-allograft	

PBSCT, peripheral blood stem cell transplant; ECP, extracorporeal photopheresis; TSEB, total skin electron beam; PUVA, psoralen + ultraviolet A; SDT, skin-directed therapy including topical emollients, steroids, mechlorethamine, carmustine, bexarotene gel, UVB/PUVA, superficial radiotherapy. Stage III includes Sézary syndrome, although some cases of Sézary syndrome will be stage IVA. ECP ideal for those patients with peripheral blood involvement. *Not yet licensed in Europe.

A/level IIii) The use of high-dose chemotherapy is not indicated in the management of lymphomatoid papulosis. However, a small proportion of patients (4%) will develop other forms of lymphoma including mycosis fungoides, Hodgkin's disease and large cell anaplastic lymphoma. Skin-directed treatment of primary cutaneous large cell anaplastic lymphoma is also appropriate unless patients develop very extensive cutaneous involvement or systemic disease.[63]

Other primary cutaneous T-cell lymphomas

This group of primary cutaneous T-cell lymphomas are poorly defined in terms of clinicopathological features, but the CD30-negative large cell pleomorphic, anaplastic and immunoblastic variants all have a poor prognosis. There have been no significant therapeutic studies. When disease is restricted to the skin radiotherapy may be indicated, but systemic dissemination is likely and most patients will require some form of multiagent chemotherapy, although responses are likely to be poor. Primary cutaneous extranodal NK-like/T-cell lymphomas (nasal type) have a poor prognosis.[2] Primary subcutaneous panniculitis-like T-cell lymphomas are rare but also have a poor prognosis with a high incidence of systemic involvement and haemophagocytosis either at diagnosis or shortly afterwards.[2] Extranodal NK-like/T-cell, blastic NK-cell and subcutaneous T-cell lymphomas can have a cytotoxic phenotype and may show angiocentricity. These categories of CTCL will invariably require systemic chemotherapy and skin-directed therapy alone is not indicated. (*Grade A/level III*)

Conclusions

The few randomized studies in CTCL so far clearly indicate that in early stage disease skin directed treatment represents the most appropriate therapy. Long-term cure may be achieved in localized disease such as pagetoid reticulosis but patients with multifocal early stage disease, as present in most cases of mycosis fungoides, are only likely to achieve a short-term clinical response with recurrent disease for many years and, in the majority of cases, a normal life expectancy. Therefore potentially toxic and aggressive therapies ought to be avoided.

In contrast, patients with later stages of mycosis fungoides have a poor prognosis and the absence of large well-designed randomized controlled studies at present is reflected by a lack of consensus regarding treatment. CTCL is a very radiosensitive tumour and both superficial radiotherapy and TSEB therapy are invaluable treatments for all patients and especially those with later stages of disease. A striking feature of the published studies of a wide variety of different therapies to date is an overall response rate of approximately 30% and a complete response rate of 10%. Single and multiagent

chemotherapy regimens produce a higher complete response rate (approximately 30%) but this tends to be short-lived (median duration 3–41 months). This suggests that, for most patients, none of these therapies has so far had any significant impact on disease outcome and that the same minority of patients with responsive disease are benefiting. Ideally all patients with late-stage disease should be entered into appropriate clinical trials. It is also critical to ensure that the individual patient's quality of life is considered when therapeutic options are discussed and that patient expectations are realistic. Palliative care should be considered for all patients with resistant late-stage disease and those with poor performance status (ECOG > 2).

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Appendix A: WHO classification relating to primary cutaneous T-cell lymphomas

Indolent

- Mycosis fungoides (pagetoid reticulosis/follicular mucinosis)
- Primary cutaneous large cell anaplastic CD30+ lymphoma (pleomorphic/immunoblastic*)
- Lymphomatoid papulosis.

Aggressive

- Sézary syndrome
- Peripheral T-cell lymphoma (large cell CTCL CD30– pleomorphic/immunoblastic*).

Provisional

- Granulomatous slack skin
- Peripheral T-cell lymphoma (CTCL small/medium cell—pleomorphic*)
- Subcutaneous panniculitis like T-cell lymphoma.

(The EORTC classification of primary cutaneous lymphomas[1] recognizes the clinicopathological entities indicated*. Although these other entities are not clearly defined in the WHO classification, some of these primary cutaneous large cell CD30– and small/medium cell pleomorphic lymphomas may represent primary cutaneous extranodal NK-like/T-cell lymphomas (nasal type), blastic NK-cell lymphomas or uncharacterized peripheral T-cell lymphoma as described in the WHO classification.)

Appendix B: clinical staging system for cutaneous T-cell lymphoma

TNM classification

T1: Patches or plaques < 10% body surface area
T2: Patches or plaques > 10% body surface area
T3: Tumours
T4: Erythroderma
N0: No palpable nodes
N1: Palpable nodes without histological involvement (dermatopathic)
N2: Nonpalpable nodes with histological involvement
N3: Palpable nodes with histological involvement
M0: No visceral disease
M1: Visceral disease
B0: No haematological involvement
B1: Sézary count > 5% of total peripheral blood lymphocytes

Bunn & Lambert system

Stage IA: T1 N0
Stage IB: T2 N0
Stage IIA: T1/2 N1
Stage IIB: T3 N0/1
Stage III: T4 N0/1
Stage IVA: T-any N2/3
Stage IVB: T-any N-any M1

(Both staging systems are complementary. Sézary syndrome patients can be stage III, IVA or IVB. The Bunn & Lambert system does not adequately address the issue of peripheral blood involvement in CTCL.)

Appendix C

The consultation process and background details for the British Association of Dermatologists guidelines has been published elsewhere.[66,67]

Strength of recommendations

A There is good evidence to support the use of the procedure.
B There is fair evidence to support the use of the procedure.
C There is poor evidence to support the use of the procedure.
D There is fair evidence to support the rejection of the use of the procedure.
E There is good evidence to support the rejection of the use of the procedure.

Type of evidence

I Evidence obtained from at least one properly designed, randomized controlled trial.
II-i Evidence obtained from well designed controlled trials without randomization
II-ii Evidence obtained from well designed cohort or case–control analytic studies, preferably from more than one centre or research group.
II-iii Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the introduction of

penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.
IV Evidence inadequate owing to problems of methodology (e.g. sample size, or length or comprehensiveness of follow-up or conflicts of evidence).

Appendix D: Details of ongoing trials as at April 2003

European Organization for Research and Treatment of Cancer

1 Protocol 21011: a phase III randomized study comparing PUVA with combined PUVA and oral bexarotene in stage IB–IIA mycosis fungoides.
2 Protocol 21012: a phase II study assessing liposomal doxorubicin in stage IIB–IVA mycosis fungoides.

Multicentre studies

1 Protocol 93-04-11: a randomized study assessing two different dosage schedules for denileukin diftitox in stage IB–III CD25+ CTCL compared with placebo.
2 Protocol 93-04-14: an open study assessing denileukin diftitox (18 μg kg^{-1} day^{-1}) in stage IB–III CD25– CTCL patients.
3 Protocol Hx-CD4-007: an open study assessing a fully humanized anti-CD4 antibody in stage IB–IIA primary CTCL.
4 Protocol Hx-CD4-008: an open study assessing a fully humanized anti-CD4 antibody in stage IIB–IVB primary CTCL.