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CONTINUING PROFESSIONAL DEVELOPMENT PROGRAM

Management of the primary cutaneous lymphomas

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SUMMARY

Cutaneous lymphomas are rare and, although some are a manifestation of systemic lymphoma, the majority arise primarily from the skin. These primary cutaneous lymphomas comprise both T- and B-cell subtypes and represent a wide spectrum of disorders, which at times can be difficult to diagnose and classify. Classical therapeutic strategies include topical corticosteroids, phototherapy, radiotherapy, retinoids, extracorporeal photopheresis, topical chemotherapy, systemic chemotherapy and biological response modifiers. Newer therapies include the synthetic retinoid bexarotene, the immunotoxin conjugate denileukin diftitox, interleukin-12 and monoclonal antibodies such as alemtuzumab and rituximab.

Key words: B-cell, mycosis fungoides, phototherapy, radiotherapy, Sézary syndrome, T-cell.

INTRODUCTION

Primary cutaneous lymphomas comprise both T-cell (≥75%) and B-cell lymphomas and are rare conditions representing 2% of all lymphomas with an annual incidence of 0.3–1 per 100 000.[1,2] The most common form of cutaneous T-cell lymphoma (CTCL) is mycosis fungoides (MF), which is typically found in adults of 40–60 years of age in all races, with men afflicted by the disorder twice as commonly as women. Primary cutaneous B-cell lymphomas (PCBCL) comprise, after gastrointestinal, the second largest group of extranodal B-cell lymphomas.

The aetiology and clinical features of the cutaneous lymphomas have been thoroughly reviewed recently,[1,3,4] and the present review will focus on the treatment of these diseases. The vast majority of cases can be diagnosed on haematoxylin and eosin (H&E) sections with appropriate immunophenotyping, most commonly by immunohistochemistry and in some cases by flow cytometry.[5] Furthermore, review by a pathologist colleague experienced in these disorders is strongly recommended and the need for clinicopathological correlation cannot be overemphasized. Molecular analysis examining for the presence of a clonal T-cell receptor (TCR) gene rearrangement by polymerase chain reaction (PCR) on fresh and formalin-fixed tissue is useful, particularly in difficult cases.[6,7] However, the absence of a TCR gene rearrangement does not exclude the diagnosis; reasons for a false negative include inadequate tissue (insufficient DNA), a small population of malignant cells beyond the sensitivity of the assay, a TCR gene rearrangement that occurs outside the area assessed by the consensus primers, or 'true' natural killer cell lymphomas, which do not have a TCR. False positives can occur in up to 20% or more of cases,[6,7] and typically occur if the PCR reaction is overly sensitive (excessive cycles of PCR reaction and detection of non-clonal TCR gene), which underlines the need for these assays to be performed in a laboratory with scientists experienced in these techniques. Unfortunately, in borderline cases, where molecular studies are likely to be most helpful, the likelihood of detecting a TCR gene rearrangement can be as low as 20%.[6] B-cell clonal populations can be assessed by the presence of immunoglobulin heavy chain (IgH) gene rearrangements and/or the presence of specific molecular translocations (e.g. IgH/*bcl*-2).

Before embarking on this review it is worthwhile to comment on the current controversies surrounding the classification of these disorders.[8] Briefly, the two most widely used classifications are the World Health Organization (WHO)[9] and the European Organization for Research and Treatment of Cancer (EORTC)[10] (Tables 1–3). The authors recommend that pathologists make every attempt to classify these conditions according the WHO classification, which can encompass all the conditions and aligns the cutaneous lymphomas

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with the broader systemic lymphoproliferative conditions.[8] One disadvantage of the WHO classification is that, unlike the EORTC classification, it does not divide the entities according to clinical behaviour. In this review, the majority of the entities will be classified according to the WHO classification and also correlated with the EORTC classification.

Cutaneous T-cell lymphomas are classified into four clinical stages based on the TNM classification[11] (Table 4,5). Skin patches and plaques occur in stage I, the presence of clinically evident lymphadenopathy without pathological nodal infiltration and/or cutaneous tumours characterize stage II, generalized erythroderma characterizes stage III, and pathologically positive lymph nodes and/or visceral disease characterize stage IV.[1,4,10] Although this classification system can be applied to all the cutaneous lymphomas, most of the data correlating stage with prognosis relates to the most common form, MF, which is typically a chronic, slowly progressive disease of 10–20 years duration (see subsequent section).

There is no specific staging system for PCBCL. Indeed, if the disease has systemic (nodal, marrow or visceral) involvement it is frequently reclassified as a systemic lymphoma with secondary skin involvement.[11] Nonetheless, if the disease is felt to arise primarily from the skin it still should be staged, like other non-Hodgkin's lymphomas (NHL), according to the standard Ann Arbor criteria with isolated lesions considered as stage I and multifocal lesions as stage IV.

The wide array of clinical presentations and possible treatment modalities makes the treatment of the cutaneous lymphomas complex. Indeed, there are no simple treatment algorithms to follow. A summary of treatments for the various forms of cutaneous lymphoma are summarized in Table 6a,b, with a more detailed explanation in the text.

Table 1 World Health Organization classification of lymphoid neoplasms (excluding Hodgkin's disease)[9]

B-cell neoplasms
Precursor B-cell neoplasms
Precursor B lymphoblastic leukaemia/lymphoma
Mature B-cell neoplasms‡
Chronic lymphocytic leukaemia/small lymphocytic lymphoma
B-cell prolymphocytic leukaemia
Lymphoplasmacytic lymphoma
Splenic marginal zone lymphoma
Hairy cell leukaemia
Plasma cell myeloma
Monoclonal gammopathy of undetermined significance
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Primary amyloidosis
Heavy chain diseases
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma)
Nodal marginal zone B-cell lymphoma
Follicular lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Mediastinal large B-cell lymphoma
Intravascular large B cell lymphoma
Primary effusion lymphoma
Burkitt's lymphoma/Burkitt's cell leukaemia
Mature T-cell and NK cell neoplasms
Leukaemic/disseminated
T-cell prolymphocytic leukaemia
T-cell granular lymphocytic leukaemia
Aggressive NK cell leukaemia
Adult T-cell lymphoma/leukaemia
Cutaneous
Mycosis fungoides‡
Sézary syndrome
Primary cutaneous anaplastic large cell lymphoma‡
Lymphomatoid papulosis
Other extranodal
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Nodal
Angioimmunoblastic T-cell lymphoma
Peripheral T-cell lymphoma, unspecified
Anaplastic large-cell lymphoma
Neoplasm of uncertain lineage and stage of differentiation
Blastic NK cell lymphoma

†B- and T-/NK-cell neoplasms are grouped according to major clinical presentations (predominantly disseminated/leukaemic, primary extranodal, predominantly nodal). ‡See Table 2 for variants. NK, natural killer.

PRIMARY CUTANEOUS T-CELL LYMPHOMAS

Mycosis fungoides

The management of MF needs to be individualized, with particular consideration given to the stage of the disease, the symptoms, the age and the performance status of the patient. The interval between the onset of symptoms and the establishment of a histological diagnosis frequently takes many years, often requiring repeated biopsies.[2] Indeed, for patients in whom MF is suspected, and there are a limited number of patch-stage lesions, this approach is very reasonable and avoids embarking on numerous investigations in a disease that is indolent and where outcome is not altered by aggressive early intervention.

Prognosis

The most important factor in planning management and determining prognosis is the stage of the disease. Indeed, the vast majority of patients with early-stage disease (stages IA,

Table 2 World Health Organization classification: mature T-cell neoplasms, cutaneous types: variants and subtypes[9]

MF variants
Pagetoid reticulosis
MF-associated follicular mucinosis
Granulomatous slack skin
Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
Primary C-ALCL
LyP (types A and B)
Borderline lesions: LyP type C and C-ALCL, LyP-like histology

C-ALCL, cutaneous anaplastic large cell lymphoma; LyP, lymphomatoid papulosis. MF, mycosis fungoides.

IB, IIA) do not progress to more advanced-stage disease,[2,12] and patients presenting with isolated patch or plaque disease (stages I and IIA) have a median survival of more than 12 years. Moreover, patients with stage IA disease do not appear to have a decreased survival when compared with an age-, sex-, and race-matched population.[12] Patients with advanced-stage disease (stages IIB, III and IVA) with tumours, erythroderma, and lymph node or blood involvement but no visceral involvement have a median survival of 5 years from the time of presentation. Patients with visceral involvement (stage IVB) have a median survival of only 2.5 years or less.[4,10,12,13]

Although most patients with early-stage disease (patches or plaques confined to the skin) have an indolent course, progression to cutaneous tumours, nodal or visceral disease can occur. Cutaneous tumours can develop either as increasing depth of the small atypical lymphocytes of MF or as a result of large-cell transformation. Large-cell transformation is defined as large cells (≥4× the size of a small lymphocyte) in more than 25% of the infiltrate or if these cells form microscopic nodules.[14,15] There is a variable incidence of 8–39% reported and it is associated with a very poor prognosis.[14–16] In one series of 115 patients (of which 26 transformed), the cumulative risk of MF large-cell transformation was 39% at 12 years, with the risk of transformation related to the presence of stage IIB–IV (31% compared with 14%), tumour-stage disease, elevated β2 microglobulin and elevated lactate dehydrogenase (LDH). In this study, the median survival from the diagnosis of transformation was only 19.4 months.[14] In another series of 45 patients with transformed disease, the median survival was 22 months; older patients (>60 years) and systemic spread following transformation was associated with a worse prognosis.[15] Systemic spread occurs in over one-third of patients with transformed disease with the potential to involve extranodal sites.[16] Interestingly, some patients have histological transformation preceding clinical progression; thus the value of following patients with 'surveillance' biopsies looking for histological transformation warrants further investigation.[15] Close clinical monitoring is particularly relevant in patients with MF who present at a young age (with risk of transformation increasing over time) and those with more advanced stage (≥stage IIB) disease.

Table 3 European Organization for Research and Treatment of Cancer classification for primary cutaneous lymphomas. Adapted from[10]

Primary CTCL	Primary CBCL
Indolent	*Indolent*
MF	Follicle centre cell lymphoma
MF + follicular mucinosis	Immunocytoma (marginal zone B-cell lymphoma)
Pagetoid reticulosis	
Large-cell CTCL, CD30+	*Intermediate*
Anaplastic	Large B-cell lymphoma of the leg
Immunoblastic	
Pleomorphic	
Lymphomatoid papulosis	
Aggressive	
Sézary syndrome	
Large-cell CTCL, CD30–	
Immunoblastic	
Pleomorphic	
Provisional	*Provisional*
Granulomatous slack skin	Intravascular large B-cell lymphoma
CTCL, pleomorphic small/medium-sized	Plasmacytoma
Subcutaneous panniculitis-like T-cell lymphoma	

CBCL, cutaneous B-cell lymphoma; CTCL, cutaneous T-cell lymphoma; MF, mycosis fungoides.

Staging investigations

For patients with patches and/or plaques with no palpable lymphadenopathy (i.e. clinically early stage I–IIA disease) extensive staging investigations are not required and usually restricted to physical examination and full blood examination (Sézary cells are very rarely detected). Occasional patients will present with locoregional lymphadenopathy, which may reflect dermatopathic changes in the node rather than true nodal involvement with MF. The authors' approach in these cases is to stage the patient with computed tomo-

Table 4 TNM Classification for mycosis fungoides / Sézary syndrome. Based on Bunn and Lamberg[11]

T_1	Limited patch/plaque (<10% of skin surface)
T_2	Generalized patch/plaque (>10% of skin surface)
T_3	Tumours
T_4	Generalized erythroderma
M_0	No visceral metastases
M_1	Visceral metastases
B_0	Atypical circulating cells not present (<5%)
B_1	Atypical circulating cells present (>5%)
N_0	No clinically abnormal peripheral lymph nodes
N_1	Clinically abnormal peripheral lymph nodes
NP_0	Biopsy performed, not CTCL
NP_1	Biopsy performed, CTCL
LN0	Uninvolved
LN1	Reactive node
LN2	Dermatopathic node, small clusters of convoluted cells (<6 cells per cluster)
LN3†	Dermatopathic node, large clusters of convoluted cells (>6 cells per cluster)
LN4†	Lymph node effacement

†Pathologically involved lymph nodes. B, blood; CTCL, cutaneous T-cell lymphoma; LN, lymph node; M, metastasis; T, tumour.

Table 5 Stage classification for mycosis fungoides / Sézary syndrome

	Staging classification
IA	T_1, N_0NP_0, M_0
IB	T_2, N_0NP_0, M_0
IIA	$T_{1,2}$, N_1NP_0, M_0
IIB	T_3, N_0NP_0, M_0
III	T_4, N_0NP_0, M_0
IVA	$T_{1\text{-}4}$, $N_{0,1}NP_1$, M_0
IVB	$T_{1\text{-}4}$, $N_{0,1}NP_{0,1}$, M_1

M, metastasis; N, node; NP, node biopsy performed; T, tumour.

graphy and bone-marrow examination (including flow cytometry and molecular analysis for T-cell receptor gene rearrangement) and if small locoregional nodes do not resolve following local skin therapy, lymph-node biopsy is performed. Conversely, if large nodes (>3–4 cm) are detected, a representative node biopsy should be performed before initiating therapy, given the major prognostic impact of such a finding and the required alteration in the therapy applied to include systemic sites. A hesitancy in performing node biopsies relates to the high incidence of skin colonization with pathogenic organisms in patients with CTCL, which increases the risk of infection following surgery.

Prognostic markers

There are currently no definitive prognostic factors beyond clinical stage for MF. Although the absence of CD7,[17] high LDH[18] large cell size, periodic acid-Schiff (PAS) inclusions and number of circulating Sézary cells (SC)[17] have been implicated as adverse prognostic markers, these features are usually associated with advanced-stage disease, leaving the problem of determining which patients with early-stage disease are destined to do poorly.

Treating early-stage (IA–IIA) mycosis fungoides

Overview

The vast majority of patients present with early-stage disease. As the use of early application of therapy does not impact on survival,[15] a non-aggressive approach to therapy is warranted, with treatment aimed at improving symptoms and cosmesis while limiting toxicity. Given that multiple skin sites are often involved, the initial treatment choices are usually topical or intralesional corticosteroids or phototherapy with PUVA or UVB. UVB is only effective in patients with patch disease and PUVA is usually required for patch/plaque disease, but it too becomes less effective as the lesions thicken. For even thicker plaques, particularly if localized, radiotherapy (RT) is effective. There is the very occasional patient who presents with truly localized MF (single lesion); whether this is curable is unknown and our approach is to treat such patients with local RT with 'curative' intent.

'Second-line' therapy for early-stage disease is often topical chemotherapy using mechlorethamine (nitrogen mustard; NM) or carmustine (BCNU). Retinoids can be

Table 6a Summary of treatment of cutaneous lymphomas

	Mycosis fungoides			
	Early stage	Advanced-stage	Sézary syndrome	Lymphomatoid papulosis
Observation	If stable			Frequent
Topical corticosteroids	Frequent	Symptomatic control	Symptomatic control	If localized
PUVA/UVB	Frequent		Symptomatic control	Second line
Topical chemotherapy	If limited number of lesions			If localized
Retinoids	Second line	If slowly progressive	If slowly progressive	
Bexarotene	Third line	If progressive	If progressive	
Interferon	Second line	If slowly progressive	If progressive	Second line
Oral methotrexate	If slowly progressive	If slowly progressive	If slowly progressive	Usual first line if therapy needed
Radiotherapy	If localized large/plaques and tumour nodules	If localized large/plaques and tumour nodules	TSEB	
Systemic chemotherapy	Third line	If progressive	If progressive	
Denileukin diftitox	Third line	If progressive	If progressive	
Extracorporeal photopheresis	If circulating Sézary cells		If progressive	

TSEB, total skin electron beam.

Table 6b Summary of treatment of cutaneous lymphomas

	Anaplastic large cell lymphoma		Follicle centre lymphoma	Diffuse large B-cell lymphoma	Marginal zone lymphoma
	CD30+	CD30-			
Radiotherapy	If localized	With chemotherapy	Routine	If localized and good prognosis	Routine if localized
Systemic chemotherapy Denileukin diftitox Extracorporeal photopheresis	If nodal or widespread	Routine	If widespread	If poor prognosis	If extensive

effective for disease refractory to topical therapies and are usually considered prior to the use of chemotherapy. Very large tumours may require orthovoltage/megavoltage RT. Total skin electron beam (TSEB) therapy is usually reserved for patients with extensive skin involvement that has failed prior therapy. The authors' experience is that TSEB is most successful in patients with relatively indolent disease, as early relapses (months) are common in patients with rapidly progressive disease.

Topical corticosteroids

Early-stage CTCL, particularly patch-stage MF, can be treated with topical corticosteroids. Class I (potent) topical corticosteroids such as betamethasone dipropionate 0.05% or mometasone furoate 0.1% are the most effective at obtaining objective disease regression.[19] Patients with stage T1 disease (limited patch/plaque with <10% of skin surface involved) have an approximately 60–65% complete response (CR) rate (biopsy proven) and a 30% partial response (PR) rate. Patients with T2 disease (generalized patch/plaque with >10% of skin surface involved) have a 25% CR rate and a 57% PR rate. Topical corticosteroids have CR rates similar to other forms of skin-directed therapies.[19–22] Intralesional corticosteroids can be effective in treating thicker CTCL lesions such as plaques or tumour deposits.

Phototherapies

Cutaneous T-cell lymphomas can be treated effectively with the various forms of phototherapies including PUVA, UVB and electron beam radiation therapy (see below). PUVA therapy can be useful in treating patch-and-plaque-stage CTCL; however, tumour-stage disease is less responsive. Bath PUVA therapy has also been shown to be effective.

Response rates to PUVA therapy in patients with patch disease are high, with CR rates of approximately 58–83% and overall response rates of up to 95%.[20,23,24] Furthermore, remission is often prolonged, with a reported mean duration of 43 months.[20] Maintenance treatment with weekly or fortnightly therapy can be effective in maintaining remission. PUVA therapy is generally well tolerated; however, acute side-effects include nausea (from the oral psoralens) or photosensitivity. Long-term side-effects are acceleration of solar damage and an increased rate of skin malignancies including squamous cell skin cancer and melanoma.[25–27]

More recently, UVA1 (340–400 nm) has been reported to be as effective as PUVA for stage IA and IB disease.[28] UVB is also effective for CTCL, particularly for patch and thin plaque disease. Broadband UVB (300–320 nm) was initially used, and more recently narrowband UVB (311 nm) has also been shown to be effective in CTCL, although remission duration with the latter may be inferior.[29,30]

Phototherapy can also be combined with other treatments. PUVA has been reported to achieve improved response rates when combined with interferon-alpha (IFN-α) 2b[31,32] or acitretin.[33] PUVA therapy has also been used as a salvage or maintenance therapy after TSEB.[34]

Topical chemotherapy

Therapy for CTCL is frequently administered topically, particularly in early-stage disease, and active agents include NM and BCNU. However, the use of these agents can be impractical if lesions are extensive, and with long-term use carry a risk of secondary epidermal cancer. Moreover, particular care must be taken to avoid topical exposure to those carers assisting with the application of the solution or ointment. Drug hypersensitivity is reported to occur in up to 45% or more of patients treated with topical NM, particularly in solution form. Nitrogen mustard ointment reduces the incidence of allergic reactions; however, it involves considerable pharmacy preparation and consequently is not readily available.[35] Skin sensitivity occurs in up to 5% of patients treated with BCNU.

Radiotherapy

Cutaneous lymphomas are usually highly radiosensitive. Even doses as low as 4 Gy can at least temporarily control small areas of disease, but RT-induced cures of CTCL are much more elusive. In planning therapy one must consider a number of interrelated variables, including: the aim of treatment, the extent of disease, technical issues (modality, dose, fractionation, field arrangement), concurrent treatments and, of course, patient-specific factors.

Treatment is usually aimed at improving symptoms and cosmesis, although in truly localized disease the intent of therapy may be curative. Indeed, the extent of skin involvement is the major determinant for curative potential. There is a clear gradient of both diminishing likelihood of CR and length of remission with increasing stage of disease; patients with T1 disease have a >80% CR rate with RT (either local-field or TSEB therapy), compared with 20–30% CR rates for T4 disease. Five-year relapse-free survival rates with radiation alone are 40–60% for T1 disease, but <10% for T4 disease.[34,36–41] Irrespective of stage and curability, however, RT can provide excellent palliation of troublesome symptoms of CTCL such as pruritus, scaling and ulceration.

Target volume. For most patients the target volume is the epidermis and/or dermis, that is, the maximum depth of interest is only 5 mm from the skin surface unless there are tumours or deep ulcers. Most lesions may therefore be treated with very soft (low penetrance) beams: superficial X-ray therapy (50–145 kvp) for small areas, or 4–9 MeV electron beams for larger areas. Higher energy beams (orthovoltage/megavoltage) are occasionally necessary for thicker lesions.

The technique of TSEB therapy has been developed for the treatment of patients with extensive disease. It is a complex technique designed to overcome the variation in dose at field margins that otherwise occurs with fixed fields and a circumferential target. It requires the use of either multiple field arrangements (usually six fields) or a rotational technique, with 'patching' or 'boosting' using small additional fields for areas of under-dosing and self-shielding, for example the vertex of the scalp, the soles of the feet, the perineum and the upper medial thighs.[42–48] During the 1970s and 1980s, TSEB to doses of approximately 36 Gy was widely applied, not only for patients with extensive disease but also

for patients with T1 and T2 disease, as it was thought that this might offer a higher chance of cure. Unfortunately, although relapse-free survival was superior in these patients compared with those treated with local-field RT or other less aggressive approaches, long-term disease-specific and overall survival were not improved.[36,37,49,50] The technique is now generally limited to patients with T3/4 disease, and to those who are no longer responding to topical therapies.

Dose. Although very small doses of radiation can provide effective palliation of CTCL lesions, there does appear to be a dose–response relationship for complete remission. Doses of 35–40 Gy are associated with higher CR rates than doses of <25 Gy, particularly with more advanced stages of disease.[36,49–52] There is no information for doses of >40 Gy, but good evidence for a dose–response relationship beyond 40 Gy for lymphomas in other sites is lacking, and particularly if large areas of skin are being irradiated, there is a reluctance to increase the dose beyond 40 Gy because of the potential for significant long-term toxicity. This is a subject that deserves further study in the context of the very aggressive disease seen in some younger patients.

Fractionation. Fraction size is dependent on a number of factors. Small fields in cosmetically insignificant areas may be hypofractionated, e.g. 30 Gy in 10 fractions, three or five times per week. However, in cosmetically sensitive areas, where large fields are being irradiated, where there is pre-existing damage to the skin, or in cases of re-treatment, doses of only 1.0–1.5 Gy per fraction may need to be used. This may result in a course of treatment taking up to 10 weeks.

Combined modality treatments. For patients with extensive and/or resistant disease, radiation has been used concurrently with a number of other treatments: PUVA, UVB, retinoids and chemotherapy. In general, these combinations increase the risk of toxicity, with little convincing evidence of additional benefit beyond their sequential application on relapse.[13,53,54] A dose of radiation that can be safely delivered by itself with minimal toxicity may result in marked erythema or desquamation of skin when administered concurrently with chemotherapy. Resultant modifications to the radiation schedule and treatment breaks may compromise the effectiveness of the RT. Total skin electron beam therapy followed by adjuvant PUVA does lead to a significant benefit in disease-free survival, but not in overall survival.[34] One combined modality approach for patients with extensive disease that the authors have found to have promising efficacy is the use of two to three courses of chemotherapy, for example, high-dose methotrexate to reduce disease to clinically minimal levels before proceeding with TSEB.

Patient factors. Most patients with CTCL are in good general health and may be working full-time. It is therefore desirable that the treatment impact as little as possible on their normal lifestyle. A 10-week course of treatment that is unlikely to be curative may therefore be an undue hardship if other options are available. Co-existing medical problems rarely preclude a patient from RT, but there are some contraindications, such as scleroderma, or the inability to stand for several minutes at a time during TSEB therapy.

Retinoids

Retinoids belong to the family of steroid hormones that bind to the nuclear receptors (retinoic acid receptor, RAR; retinoid X receptor, RXR) and subsequently interact with various transcription factors such as c-Jun/c-Fos.[55] There are various isoforms of RAR and RXR (α, β and γ) that are differentially expressed in tissues. The skin contains both RAR and RXR. Non-RXR-selective retinoids such as etretinate, arotinoid, acitretin and isotretinoin (13-*cis*-retinoic acid) have been used alone or in combination with PUVA, IFN-α, or even chemotherapy and are reported to have response rates in the range of 5–65%.[32,56–66] Bexarotene is a new synthetic retinoid that selectively binds to the RXR subfamily and is formulated as either a capsule or as a topically applied gel.[67,68] In the authors' experience, bexarotene can achieve responses in chemoradiotherapy refractory patients within 1 month of treatment; however, relapse within a few months generally occur.[69] The future commercial availability of topical bexarotene may result in its use in early-stage disease in place of topical chemotherapy.

Treating advanced-stage (IIB–IV) mycosis fungoides

Overview

Treatment of advanced-stage disease (or indeed refractory early-stage disease) is more problematic and always requires a multidisciplinary approach involving a dermatologist, an oncologist/haematologist and a radiation oncologist. Although systemic multi-agent chemotherapy is often considered early in patients with advanced-stage disease, the randomized National Cancer Institute study demonstrated that combination chemoradiotherapy offered no survival benefit over 'conservative' topical therapy[13] and consequently, topical therapy should be used first where practicable, and systemic therapy should be considered in refractory or rapidly progressive disease. The type of systemic therapy depends largely on the age and the performance status of patients and the extent and the tempo of the disease. For indolent but progressive disease, IFN, a biological response modifier, can be effective with doses of 3–15 million units (MU) daily used (most commonly 5 MU daily).[70,71] The single- or multi-agent chemotherapy regimens described below are selected depending on disease characteristics and side-effect profile. The value of photopheresis is limited to patients with circulating malignant cells or clonal population detected by molecular analysis[72] (see Sézary syndrome, below). The biological regulators denileukin diftitox (DAB_{389}IL-2) and interleukin (IL)-12 tend to be used for advanced multi-relapsed disease but are not commercially available in Australia. There is limited information about the efficacy of autologous or allogeneic transplantation for MF (reviewed in[4]); however, in the authors' and others' experience,[73,74] (manuscript in preparation) there appears to be a prominent graft-versus-tumour effect in MF following allogeneic stem-cell transplantation. Given the high morbidity and mortality associated with this treatment, the role of this therapy in

younger patients with advanced-stage MF requires further investigation.

Systemic chemotherapy

In slowly progressive disease that has systemic manifestations or has proven refractory to topical therapy and/or retinoids, single-agent therapies such as low-dose oral methotrexate (15–25 mg/m^2/week), chlorambucil, cyclophosphamide or etoposide may be employed with a very low risk of side-effects. For more aggressive disease, multi-agent chemotherapy is usually considered. There is no recognized superior multi-agent chemotherapy regimen for MF and no proven advantage in using anthracyclines as initial therapy. Regimens often include one or more of cyclophosphamide, vincristine, vinblastine, prednisolone, methotrexate or mechlorethamine.[4,75,76] Other effective agents include liposomal doxorubicin[77,78] and nucleoside analogues/pathway inhibitors such as 2-chlorodeoxyadenosine, deoxycoformycin, fludarabine or gemcitabine.[79–81] Of note, combination chemotherapy increases the risk of infection in a group of patients frequently colonized with potentially pathogenic bacteria.[4]

Biological response modifiers

Newer therapies have been explored using biological regulators, including the recombinant targeted fusion protein that combines the receptor binding sequence of IL-2 with the cytotoxic A-chain and translocation B chain of diphtheria toxin (denileukin diftitox; ONTAK®; DAB_{389}IL-2).[82,83] This drug has recently been approved by the Food and Drug Administration in the USA for patients with relapsed CTCL whose tumours express the IL-2 receptor subunit (CD25). A related molecule, anti-Tac (Fv)-PE38 (LMB-2), is an anti-CD25 recombinant immunotoxin that comprises the antibody Fv fragment fused to a truncated *Pseudomonas* exotoxin, and also appears to have activity in CTCL.[84] Interleukin-12[85] and alemtuzumab (Campath-1H), the humanized monoclonal antibody targeted against CD52w (a pan-lymphocyte antigen)[86,87] have demonstrated efficacy in CTCL; however, the side-effect profile with all these biological agents is at times substantial.

SÉZARY SYNDROME

The most common definition of Sézary syndrome (SS) is one of pruritic exfoliative or infiltrated erythroderma (with histological features of CTCL) accompanied by circulating SC. Although there is no consensus as to the number of SC required to define the syndrome, most commonly a SC count $>1 \times 10^9$/L or >5% of peripheral blood leucocytes is accepted.[88–90] As SS is considered the leukaemic variant of MF, an elevated SC count should be considered an essential component of the diagnosis. Sézary syndrome has been defined as the triad of erythroderma, generalized lymphadenopathy and the presence of SC in skin and blood by WHO and EORTC, with the latter preferring the demonstration of clonal T-cells and an expanded CD4+ population in the peripheral blood as criteria rather than an absolute count of at least 1×10^9/L SC.[10] Lymphadenopathy is common, although histologically evident marrow involvement is relatively rare. Consequently, patients with SS can be classified either as stage III or IV.[4] It should be noted that circulating SC can be detected in patients with tumour deposits and extensive plaques and for prognostic purposes these patients probably should not be classified as SS.

The median survival of classic SS in one report of 62 patients was 31 months with a 5-year survival of 33.5%, with the absence of CD7, large SC and the presence of PAS-positive inclusions identified as poor prognostic markers. Among other adverse prognostic parameters on univariate analysis were a previous history of MF, high number of SC ($>2.6 \times 10^9$/L) and elevated serum LDH.[17]

Patients with SS present a difficult management problem because they often suffer from severe itch, have a high risk of infection complicating therapy and remission durations following therapy are frequently short. In general terms the treatment is similar to that of advanced-stage MF. Systemic therapy or TSEB are often required if PUVA therapy fails.

One treatment that is more effective in SS compared with other CTCL is extracorporeal photopheresis (ECP). During ECP, photosensitized peripheral blood lymphocytes are exposed to UVA radiation in an extracorporeal circuit (an apheresis machine) and continuously re-infused into the patient. Photosensitization of the lymphocytes is achieved by exposing the lymphocytes to a photosensitizing agent, such as methoxsalen, during the extracorporeal circuit. This delivers consistently precise levels of UVA energy to cells containing methoxsalen before returning the treated cells to the patient.

Photoactivated methoxsalen treatment causes an increase in antigen display by transformed lymphocytes. This increase in the expression of immunogenic peptides at the cell surface is thought to be driven by the degradation of cytoplasmic proteins into small peptides and the subsequent transport of these peptides to the major histocompatibility complex class I molecules in the endoplasmic reticulum, a process that is enhanced by methoxsalen. It is suggested that ECP increases the immunogenicity of tumour-derived peptides and that the combination of ECP-damaged neoplastic cells with antigen-presenting cells induces an enhanced cytotoxic response by autologous CD8 lymphocytes against the CD4+ T-cell clones. Apoptosis appears to be the predominant mechanism of targeted cell death.[91–99] Since the first report of the efficacy of ECP in CTCL in 1987,[100] the technology has continued to be improved and methoxsalen can now be administered into the extracorporeal circulation (as opposed to being ingested), resulting in a higher concentration of the drug.

The first trial reported that 83% of patients with erythroderma responded to photopheresis.[100] Further large phase II studies have reported the therapeutic benefit of ECP in CTCL, although the response data have been variable, ranging from 30% to 80% depending on study entry criteria, patient selection, and intervals between diagnosis and treatment.[72,96,101–111] Predictors of response include; (i) patients with a higher proportion of neoplastic cells (baseline SC count as a percentage of total white cell count)[110,111] and (ii) low baseline CD8 counts predict a poor response to ECP,[96]

although this latter predictor has been challenged recently.[111] As ECP has been used in CTCL patients refractory to all other therapies, no phase III (randomized) trials have been performed.

PRIMARY CUTANEOUS CD30 POSITIVE T-CELL LYMPHOPROLIFERATIVE DISORDERS

In the WHO classification, lymphomatoid papulosis (LyP) (types A and B), primary cutaneous anaplastic large cell lymphoma of T-cell type (ALCL) and borderline lesions are considered subtypes of primary cutaneous CD30+ T-cell lymphoproliferative disorders.[9]

Lymphomatoid papulosis

Lymphomatoid papulosis is characterized by recurrent self-healing papules or nodules. Three histological subtypes of LyP have been described.[10] Despite its histologically malignant appearance, LyP has a clinically benign course with ongoing self-healing lesions. Observation only is usually required (to determine if spontaneous resolution occurs); however, if lesions are problematic, PUVA, topical corticosteroids, NM, IFN or oral methotrexate can be considered. Oral tetracyclines have been used, but given that LyP can undergo spontaneous resolution, the benefit of such treatment is unclear.[112] Approximately 15–30% of patients will develop lymphoma, most commonly MF or Hodgkin's disease, so ongoing clinical review is required.[113,114]

Primary cutaneous anaplastic large cell lymphoma

This terminology is used by the WHO classification and the EORTC prefer the term 'large cell CTCL, CD30+' and separate out 'large-cell CTCL, CD30–' disease because of the more aggressive clinical behaviour of the latter[8] (see below). The authors' believe that patients who present with cutaneous large cell CTCL should be classified according to the WHO classification: if they are CD30+ they fall under 'primary cutaneous ALCL, CD30+', and if CD30– they fall under 'peripheral T-cell lymphoma, unspecified' and in both cases the morphological characteristics of the cells should be described by the pathologist (i.e. anaplastic, immunoblastic or plemorphic) and CD30 expression (or lack of) emphasized.

Typically, primary cutaneous CD30+ CTCL presents with solitary nodules that frequently ulcerate and may spontaneously regress (particularly after biopsy). The prognosis of CD30+ cutaneous lesions is extremely good, which is in sharp contrast to the CD30– cutaneous lesions and systemic CD30+ lymphoma. Indeed, systemic ALCL is a very different condition arising from the lymph nodes requiring management similar to other systemic lymphomas.[115] Although relapses occur in approximately 40% of patients with CD30+ CTCL, systemic dissemination occurs in only 10%, with 5–10-year survival rates exceeding 95%.[116] Consequently, therapy should be relatively non-aggressive.

Adverse prognostic features for increased risk of systemic spread include the presence of multifocal skin lesions (17%) and locoregional lymph node involvement.[116] Variant histologies do not appear to impact on prognosis.[116]

Before therapy, patients should be fully staged to determine regional-node involvement and exclude systemic ALCL. It is unknown whether localized disease is curable, but the authors' approach to localized disease (which is the most common presentation) is to use local RT. Whether this is more effective than surgery alone remains unknown; however, it is well tolerated, with negligible long-term risks. Chemotherapy is virtually never required for localized disease, but is recommended if regional nodes are involved.[116] Systemic ALCL can have secondary cutaneous involvement (15% in one series) and should be managed as for the systemic disease. Patients with CD30+ ALCL developing from pre-existing MF often have a poor prognosis.[117]

LARGE CELL CUTANEOUS T-LYMPHOMA, CD30 NEGATIVE (EORTC CLASSIFICATION)

Although in the category of 'peripheral T-cell lymphoma, unspecified' in the WHO classification, this is a separate group in the EORTC classification and this entity warrants discussion. These cases may present with localized or generalized nodules or tumours and have an aggressive clinical course. The histological appearance of CD30– ALCL may be identical to that of MF undergoing transformation into large cell lymphoma. The treatment of these tumours should be more aggressive. Once full staging is performed, the authors' approach is to manage this disease as for aggressive NHL (i.e., like diffuse large cell) such that patients receive combination anthracycline-based chemotherapy followed by involved field RT where appropriate. In general terms, RT alone would be considered inadequate.

CUTANEOUS NATURAL KILLER AND NATURAL KILLER-LIKE T-CELL LYMPHOMAS

These natural killer (NK) group of lymphomas are rare and predominantly involve the upper aerodigestive tract but may involve the skin.[118–120] These are typically aggressive NHL with skin as a secondary manifestation of systemic disease. Rarely they present as primary cutaneous disorders.[118,121,122] 'Extranodal NK/T-cell lymphoma, nasal type' most commonly presents in Asian males with localized disease (nose, nasopharynx, sinuses) and a high incidence of marrow and central nervous system involvement.[123] The systemic syndrome predominantly involves the spleen, bone marrow, liver and skin and appears closely related to aggressive NK cell leukaemias that present primarily with peripheral blood manifestations and have a variable association with Epstein–Barr virus (reviewed in[124]). Response rates in both clinical syndromes are relatively high but early relapse is a common feature and the outlook is generally poor.[123] Combination chemoradiotherapy to localized disease is recommended, with aggressive systemic therapy similar to treatment of

lymphoblastic lymphoma/leukaemia including central nervous system prophylaxis.

SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA

The lesions in this condition preferentially infiltrate the subcutaneous tissue.[8,9] Patients present with multiple subcutaneous nodules and plaques mostly on the extremities and trunk, usually in the absence of lymphadenopathy and visceral involvement. Constitutional symptoms of fever and weight loss occur occasionally and are not infrequently related to an associated haemophagocytic syndrome.[9,125] The natural history is aggressive, although nodal and systemic dissemination is rare. The outlook is generally poor even with aggressive chemotherapy, with relapse frequent.[125]

PRIMARY CUTANEOUS B-CELL LYMPHOMAS

Approximately 20–25% of primary cutaneous lymphomas are of B-cell lineage.[3,126] Differentiation from B-cell pseudolymphomas can be very difficult and often requires clinical and full pathological assessment, including immunophenotypic and immunoglobulin gene rearrangement studies.

CUTANEOUS FOLLICLE CENTRE LYMPHOMA

This is the most common (and controversial) of the PCBCL (40%). It is classified as a follicular lymphoma *variant* in the WHO system.[9] Lesions tend to be solitary or grouped nodules or plaques often localized to the scalp, forehead or back, and systemic dissemination is rare. The WHO classification uses the term 'follicle centre (FC) lymphoma' in preference to the 'follicle centre cell (FCC) lymphoma' of the EORTC. This is not a minor point and the terms cannot be used interchangeably (reviewed in[8]). Indeed, many of the lesions classified as FCC by the EORTC would now be classified as diffuse large B-cell lymphoma (DLBCL) in the WHO classification (see below).[127] Thus, clinical series that in the future use the WHO classification are more likely to 'reject' lesions with large cells and/or diffuse histology as FC lymphoma and classify them as DLBCL; consequently, such studies will need to be interpreted with caution and as not comparable to EORTC studies that include patients with large cell histology as FCC lymphoma. Conversely, large series by the EORTC have demonstrated that their classification is reproducible and, by their criteria, even tumours with more diffuse ± large cell histology can be classified within FCC and do behave in a similar clinically indolent fashion. In patients with FCC lymphoma of large cell histology, only round cell histology appears to be an adverse prognostic marker (not age, size or number of lesions).[97]

These are indolent lymphomas and, in general terms, RT is a very important component of treatment and should encompass all lesions if possible. Although some authors have recommended doxorubicin-based chemotherapy, the studies are small and the outcome appears similar to that expected with RT alone.[128] Indeed, one small study has demonstrated that for multiple lesions, RT to all involved sites was as effective as chemotherapy.[129] The use of anthracyline-based chemotherapy should be considered in patients where the disease cannot be encompassed by RT.[130] Surgery alone is not recommended. The overall survival is excellent (97% 5-year survival) but relapses occur frequently (30–60%); thus ongoing follow up is required.[3,131] Recently, the monoclonal antibody to CD20, rituximab, which is commonly used in the treatment of systemic follicular lymphomas and DLBCL, has been successfully used in cutaneous FC, FCC and DLBCL.[132]

DIFFUSE LARGE B-CELL LYMPHOMA

The WHO classifies all lesions with a diffuse infiltrate of large B-cells into this category. In contrast, there are few patients categorized as such in the EORTC classification, with most lesions being categorized as FCC lymphoma (see above). However, the EORTC recognize a specific clinical entity, primary cutaneous large B-cell lymphoma of the leg (PCLBCL-leg) as an aggressive disease confined to the legs of the elderly.[10] It is questionable whether PCLBCL-leg should be regarded as a distinct entity on the basis of site and it has been argued that the poor prognosis is likely to be related to multiple sites of involvement implying dissemination.[133] Consequently, a large European study investigated the outcomes of 145 patients with PCLBCL-leg and non-leg-PCLBCL. This study demonstrated that lesions within both groups could be separated into two broad histological types: presence or absence of round nuclei. Multivariate analysis demonstrated that adverse prognostic features were round cell morphology ($P < 0.001$), location on leg ($P = 0.002$) and >1 skin lesion at diagnosis ($P = 0.01$). Furthermore, this study was also able to clearly distinguish an inferior overall survival in the PCLBCL-leg group when compared with those classified as FCC lymphoma (all FCC had large cell histology) (52% compared with 94%, $P < 0.0001$).[134]

In planning therapy, the authors would recommend that patients should be classified as having good or poor prognosis. Poor prognosis patients, namely those with PCLBCL-leg and round cell histology (note: the authors believe there remains inadequate prognostic information to base therapy purely on number of sites) should be treated with anthracycline-based chemotherapy (if age and cardiac status allows).[128,129] The use of additional rituximab warrants further investigation.[132] The value of additional RT is unknown, but should be considered particularly if there are limited lesions. Unfortunately, the vast majority of patients relapse or have systemic progression.

Generally, good prognosis patients (i.e. histology other than round cell, not involving the leg) should be treated as for FC lymphoma, predominantly with RT. A cautionary comment: some authors have voiced a very reasonable concern that many lesions previously classified as FCC lymphoma by the EORTC will be now be labelled as DLBCL according to the WHO classification, and one potential ramification is that physicians who are less familiar with the

subtleties of the management of good prognosis PCBCL will inappropriately use chemotherapy for such patients.[135]

CUTANEOUS EXTRANODAL MARGINAL ZONE B-CELL LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE TYPE

Primary cutaneous marginal zone lymphoma (MZL) is rare, although in one series of non-nodal/non-gastrointestinal mucosa-associated lymphoid tissue lymphomas the incidence was 12.5%.[136] There is also controversy in the literature as to the appropriate nomenclature for MZL and the WHO classification would include many cases of what the EORTC group has called immunocytoma and FCC lymphoma.[137,138]

Management includes complete staging with marrow and computed tomography scan, particularly in patients with multiple disease sites. In other non-nodal/non-gastric MZL, localized RT is extremely effective and consequently, it is generally recommended to use localized RT in cutaneous MZL. However, for small localized lesions, the advantage of RT over surgical resection alone is unknown. The outcome of treatment is extremely good and although relapses can occur in ≥50% of patients, the 5-year survival is 98–100%.[129,139,140]

SUMMARY

The first step in managing cutaneous lymphomas is getting an accurate diagnosis, which always requires good communication between the clinician and pathologist. In some instances close observation and repeated biopsies may be needed. Treatment requires an individualized approach, depending largely on the stage of disease and the performance status of the patient. Overaggressive therapy with multi-agent chemotherapy should be avoided, particularly in patients with early-stage CTCL or indolent B-cell lymphomas. Exciting novel targeted-therapies are under investigation, which will add to the armamentarium of treatments for this challenging group of diseases.

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Continuing Professional Development Program

Select the most correct answers — multiple answers possible for questions 1–11

1. A false negative T-cell receptor (TCR) gene rearrangement study may be the result of:
   a. An inadequate amount of DNA in the biopsy tissue.
   b. A small population of malignant cells beyond the sensitivity of the assay.
   c. A TCR gene rearrangement outside the area assessed by the consensus primers.
   d. Use of formalin rather than fresh tissue.
   e. Excessive cycles of polymerase chain reaction.
2. Large cell transformation in patients with established mycosis fungoides:
   a. Occurs in fewer than 5% of cases.
   b. Is associated with a poor prognosis.
   c. Is defined as large cells in more than 25% of the infiltrate.
   d. Is related to decreased lactic dehydrogenase.
   e. Is associated with elevated β2 microglobulin.
3. Regarding Sézary syndrome:
   a. Diagnosis requires the demonstration of clonal T-cells in the peripheral blood.
   b. Is commonly associated with marrow involvement.
   c. Periodic acid-Schiff-positive inclusions indicate a poor prognosis.
   d. Extra-corporeal photopheresis is a more effective therapy than it is in other forms of cutaneous T-cell lymphoma.
   e. Is defined as a triad of erythroderma, generalized lymphadenopathy and Sézary cells in skin and blood.
4. Regarding lymphomatoid papulosis:
   a. It tends to run a benign course with self-healing lesions.
   b. Fifty per cent of patients go on to develop lymphoma.
   c. Active treatment is always required.
   d. It is a primary B-cell proliferative disorder.
   e. Three histological subtypes have been described.
5. Regarding topical corticosteroid use in mycosis fungoides:
   a. This is ineffective when patients reach stage T2 disease.
   b. Topical corticosteroid use has similar complete response rates to other skin-directed therapies.
   c. Intralesional corticosteroids are ineffective for plaque and tumour lesions.
   d. Approximately 60–65% of patients with T1 disease gain a complete response to this treatment.
   e. Approximately 30% of patients with T1 disease achieve a partial response to this treatment.
6. With respect to phototherapy in cutaneous T-cell lymphoma (CTCL):
   a. Narrowband UVB offers similar duration of remission to PUVA in patch and plaque stage CTCL:
   b. PUVA gives complete response rates of 40–45% in patch-stage mycosis fungoides.
   c. UVA therapy has been shown to be effective in CTCL.
   d. PUVA therapy has been reported to induce only short-term remissions.
   e. Phototherapy has been reported to have improved response rates when combined with acitretin and interferon-alpha 2b.
7. Which of the following agents may be effective for cutaneous T-cell lymphoma when given topically?
   a. Nitrogen mustard.
   b. Liposomal doxorubicin.
   c. Carmustine (BCNU).
   d. Retinoids.
   e. Corticosteroids.
8. Which of the following therapies has established utility in the systemic treatment of cutaneous T-cell lymphoma?
   a. Total skin electron beam therapy.
   b. Photopheresis.
   c. Methotrexate.
   d. Cylcophosphamide.
   e. Denileukin diftitox.
9. With respect to radiotherapy for cutaneous T-cell lymphoma:
   a. Doses of <25 Gy are associated with high complete cure rates.
   b. Long-term toxicity may be associated with doses >40 Gy.
   c. For small lesions in cosmetically significant areas, doses of 3 Gy per fraction three or five times per week to a total of 30 Gy are suitable.
   d. Concurrent administration of radiotherapy with chemotherapy may increase local toxicity.
   e. Localized lesions with CD30+ histology are associated with good long-term local control.
10. Regarding primary cutaneous B-cell lymphoma, the following are typically associated with a favourable prognosis:
    a. Marginal zone lymphoma.
    b. Diffuse large B-cell with round cell histology.
    c. Diffuse large B-cell tumours of the leg.
    d. Follicle centre lymphoma.
    e. More than one skin lesion at diagnosis.
11. Primary cutaneous anaplastic CD30+ cutaneous T-cell lymphoma:
    a. Typically presents as multiple nodules.
    b. Ulceration is infrequent.
    c. Has a worse prognosis that CD30– disease.
    d. Spontaneous regression may be observed after a skin biopsy.
    e. Systemic dissemination occurs in 40%.

Directions for questions 12–23. For each numbered item, choose the appropriate lettered item. There is only one correct answer to be chosen, but the same letter can be chosen more than once in any questions.

With respect to questions 12–15:
   a. Bexarotene.
   b. Alemtuzumab (Campath-1H).
   c. Radiotherapy.
   d. Denileukin diftitox (Ontak).

12. Binds to panlymphocyte antigen CD52w.
13. Contains elements of the diphtheria toxin.
14. Synthetic retinoid with retinoid X receptor binding activity.
15. Contraindicated in patients with scleroderma.

With respect to questions 16–19:
   a. CD30+ cutaneous T-cell lymphoma.
   b. Adverse prognostic marker in Sézary syndrome.
   c. Lymphomatoid papulosis.
   d. Natural killer cell lymphoma.

16. Increased in Asian men.
17. Previous history of mycosis fungoides.
18. Relapses occur in approximately 40%.
19. Aggressive histology is discordant with clinical behaviour.

With respect to questions 20–23:
   a. Cutaneous follicle centre lymphoma.
   b. Subcutaneous panniculitis-like T-cell lymphoma.
   c. Mycosis fungoides.
   d. Lymphomatoid papulosis.

20. CD30+ T-cell lymphoproliferative disorder.
21. Often localized to the scalp.
22. Constitutional symptoms related to associated haemophagocytic syndrome.
23. Chronic slowly progressive disease of 10–20 years duration.

The correct answers for the questions published in Vol. 44, No. 3, are as follows:

1. a, d	9. b, c, e	17. d
2. b, e	10. a, b, e	18. a, c
3. b, d, e	11. a, b, c, e	19. b
4. a, d, e	12. b	20. b
5. c, d, e	13. c	21. c
6. a, b, c, e	14. d	22. d
7. a, b, e	15. a	23. a
8. a, c, e	16. c	

The Australasian College of Dermatologists

Continuing Professional Development Program
Category I

Australasian Journal of Dermatology
Volume 44, No. 4, 2003

Name: ..... **CPDP No.:** .....

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Questions 1–11
Circle the most appropriate answers — multiple answers possible. Each question must have all correct answers circled in order to receive points.

1.	A	B	C	D	E
2.	A	B	C	D	E
3.	A	B	C	D	E
4.	A	B	C	D	E
5.	A	B	C	D	E
6.	A	B	C	D	E
7.	A	B	C	D	E
8.	A	B	C	D	E
9.	A	B	C	D	E
10.	A	B	C	D	E
11.	A	B	C	D	E

Questions 12–23
Circle the correct answer.

12.	A	B	C	D
13.	A	B	C	D
14.	A	B	C	D
15.	A	B	C	D
16.	A	B	C	D
17.	A	B	C	D
18.	A	B	C	D
19.	A	B	C	D
20.	A	B	C	D
21.	A	B	C	D
22.	A	B	C	D
23.	A	B	C	D

Pass Mark: 75% (if you obtain this mark or higher you will be granted 1.5 hours Category 1 CPDP credit).

If you feel the need to indicate ambiguity in a question, please do not write comments on the answer sheet.

Please return your answer sheet to College by 1 January 2004. Answer sheets received after this date will not be accepted.