GUIDELINE FOR ASSESSMENT AND MANAGEMENT OF T CELL NEOPLASMS.

New Zealand Lymphoma Study Group June 2013

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1. Introduction/Overview

T cell lymphomas are a heterogeneous group of rare disorders. The WHO classification includes malignant neoplasms of immature precursor T cells, those of post thymic mature T cells as well as those of natural killer (NK) cells. As these conditions are rare, the level of evidence base for their treatment is suboptimal having been based largely on data obtained from usually retrospective cohort studies, phase II clinical trials and expert opinion. Central clinico-pathological review is required for accurate diagnosis and treatment planning. Many types of T cell lymphoma are associated with a poor prognosis and innovative treatments are needed as well as efforts to treat patients within multi-centre international phase III clinical trials. This guideline frequently refers to the contents of other guidelines recently produced by expert national groups including those of the US National Comprehensive Cancer Network (NCCN), the British Committee for Standards in Haematology (BCSH) and the European Society of Medical Oncology (ESMO).

2. Classification and Epidemiology.

This is based on the 4th WHO classification of Tumours of Haematopoietic and Lymphoid Tissues published in 2008, the WHO-EORTC classification for cutaneous lymphomas published in 2005 and is reproduced in list form below. They are also commonly classified into those with predominantly leukaemic (disseminated), nodal, extranodal or cutaneous presentations (Table 1).

Table 1. WHO 2008: T-cell and NK-cell neoplasms.

**Precursor T cell lymphomas**
- T cell Lymphoblastic lymphoma (T-LBL)
- T cell lymphoblastic leukaemia (see acute leukaemia section)

**Predominant Nodal Localisation**
- Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS)
- Angioimmunoblastic T-cell lymphoma (AITL)
- Anaplastic large cell lymphoma (ALCL), ALK+
  - Anaplastic large cell lymphoma (ALCL), ALK–*

**Predominant extranodal. Non-cutaneous Localisation**
- Extranodal NK/T cell lymphoma, nasal type (ENKTCL)
- Enteropathy-associated T-cell lymphoma (EATL)
Hepatosplenic T-cell lymphoma (HSTCL)
Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS)

**Mature T cell leukaemias. Leukaemic localisation**

T-cell prolymphocytic leukaemia (T-PLL)
T-cell large granular lymphocytic leukaemia (T-LGL)
Adult T-cell leukaemia/ lymphoma (ATLL)
Chronic lymphoproliferative disorder of NK-cells (CLPD-NK)*
Aggressive NK cell leukaemia

*Systemic EBV+ T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)*
*Hydroa vacciniforme-like lymphoma*

**Primary cutaneous localisation**

Mycosis fungoides (MF) and Sézary syndrome (SS)
Primary cutaneous CD30+ T-cell lymphoproliferative disorders
  Primary cutaneous anaplastic large cell lymphoma (PC ALCL)
  Lymphomatoid papulosis (LyP)
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)
*Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (AECTCL)*
*Primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL)*
*Primary cutaneous small/medium CD4+ T-cell lymphoma (SMPTCL)*
*(Blastic plasmacytoid dendritic cell (BPDC) neoplasm)*

*These represent provisional entities or provisional subtypes of other neoplasms. Diseases shown in italics are newly included in the 2008 WHO classification.*
### International T-Cell Lymphoma Project: Frequency of PTCL Subtypes

- Peripheral T-cell lymphoma: 25.9%
- Angioimmunoblastic: 18.5%
- NK/T-cell lymphoma: 12.2%
- Adult T-cell leukemia/lymphoma: 10.4%
- ALCL, ALK+: 9.6%
- ALCL, ALK-: 6.6%
- Enteropathy-associated T cell: 5.5%
- Primary cutaneous ALCL: 4.7%
- Hepatosplenic T cell: 4.7%
- Subcutaneous panniculitis-like: 3.0%
- Unclassifiable PTCL: 2.5%
- Other disorders: 0.9%


### PTCL Prognosis by Subtype

- OS varies according to subtype and median OS ranges from 1-3 yrs


### 3. Assessment of T-Cell Neoplasms

This is based on general principles as for other malignancies. The differential diagnosis is driven by clinical features and initial morphological assessment. Subsequent diagnosis is usually confirmed by selected application of immunohistochemistry panels and genetic studies as required. These features are finally reviewed at a lymphoma multidisciplinary meeting. Various algorithms have been devised for assistance in the diagnostic process and one is shown overleaf.
4. **T cell Lymphoblastic lymphoma (T-LBL) in adults**

**Notes**
- T-LBL is a neoplasm of immature T cells postulated to arise from thymic T cells at varying stages of maturation. There is a significant biological and clinical overlap between neoplasms diagnosed as LBL and acute...
lymphoblastic leukemia (ALL). By convention, the word “lymphoma” is used if there is a bulky lesion in the mediastinum or elsewhere, with no or minimal evidence of peripheral blood (PB) and BM involvement. In general, a threshold of <25% BM blasts is used for defining lymphoma.

- For T-ALL see acute leukaemia section.

- Biologic and therapeutic aspects differ between T-LBL and T-ALL, making this discrimination important. There are GEP and immunophenotypic differences between T-ALL and T-LBL and in terms of therapy additional mediastinal irradiation seems to be beneficial in T-LBL. Strategies for stem cell transplantation (SCT) in T-LBL and T-ALL also differ. Autologous SCT in complete remission (CR) in T-LBL gives a 70% survival rate, which is similar to chemotherapy alone, whereas, the non-cortical subtypes of T-ALL have a poor outcome with chemotherapy alone and seem to benefit from allogeneic transplantation in first CR.

- T-LBL patients are usually males in their teens to twenties who present with lymphadenopathy in cervical, supraclavicular and axillary regions (50%), or with a mediastinal mass (50–75%) which is usually anterior, bulky, and associated with pleural effusions, superior vena cava syndrome, tracheal obstruction, and pericardial effusions. Stage IV disease (80%), B symptoms (50%) and elevated LDH levels are common but extranodal disease (e.g. skin, testis, bone involvement or hepatosplenomegaly is less common. Patients develop later BM infiltration and leukemia. Cerebrospinal fluid evaluation is essential to rule out CNS involvement that is uncommon at presentation (5–10%), except for patients with BM involvement, where a high incidence of CNS infiltration is found.

- The differential diagnosis of T-LBL from a peripheral-T cell lymphoma relies on its expression of non-lineage-specific immature markers, such as TdT or CD99, or in some cases, CD34 and CD1A. T-ALL/LBL can be split into pre-cortical, cortical and post cortical immuno-phenotypes with the cortical type being more likely in LBL; eg early or pro-T (cCD3+, Cd7+, CD2−, CD1a−, CD4−, CD8−, CD34±); pre-T (cCD3+, Cd7+, CD2+, CD1a−, CD4−, CD8−, CD34±); cortical-T (cCD3+, Cd7+, CD2+, CD1a+, CD4+, CD8+, CD34−), and medullary-T (cCD3+, Cd7+, CD2+, CD1a−, CD4±, CD8+, CD34− and surface CD3+). T-LBL almost always shows clonal rearrangements of the T-cell receptor beta or gamma chain genes, but there is simultaneous presence of clonal rearrangements of the Ig heavy chain. Therefore, these rearrangements are not helpful for lineage assignment. Cytogenetic abnormalities are frequent in T-LBL patients (50–70%); the most common involve 14q11-13 the site of TCR alpha/delta, including inv(14)(q11;q32) and deletions or translocations involving chromosomes 9,10 and 11 corresponding to sites of TCR alpha, beta and gamma-subunit genes found in 47% of T-LBL. Translocation (9;17)(q34;q23) occurs only in LBL (usually in childhood) and carries a poor prognosis.
Management recommendations

- Dose intensity of treatment is important in T-LBL and improved results have come following the use of ALL type regimens. Adult patients do less well compared to children and ongoing issues include the optimal strategies for CNS prophylaxis, treatment of mediastinal disease and selection of patients for either autologous or allogeneic stem cell transplantation. The current Hoelzer protocol for T-LBL is recommended (GMALL T-LBL 1/2004), adapted for local use. This incorporates application of a shortened and intensified induction therapy and new consolidation cycles, prophylactic mediastinal irradiation with a dose of 36 Gy and extension of therapy duration to 1 year. The protocol also recommends collection of stem cells for autologous SCT in patients with incomplete therapy response / relapse and in Germany is prospectively evaluating the role of MRD in patient outcome.

![Diagram showing treatment protocol for T-LBL](image)

**PREDOMINANT NODAL T-NHLs**

5. Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS)

**Notes**

- PTCL-NOS is the largest group of T-cell lymphomas, accounting for around half of the cases seen. It is a heterogeneous group as assessed by GEP but at the present time it is used to encompass the large proportion of T-cell malignancies that do not fall into the more distinct diagnostic groups recognized in the WHO classification. They are aggressive lymphomas, mainly of nodal type, but extranodal involvement is common.
- The 5-year failure-free survival (FFS) and OS is about 20%.
- A prognostic index for PTCL-NOS (PTCL-U) is available based on age > 60, raised LDH levels, PS ≥2 and bone marrow involvement (vide infra).
<table>
<thead>
<tr>
<th>No of RFs</th>
<th>Prognostic Gp</th>
<th>5 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>62%</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>53%</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>33%</td>
</tr>
<tr>
<td>3 or 4</td>
<td>4</td>
<td>18%</td>
</tr>
</tbody>
</table>

**Importance of Stratifying Patients by Prognostic Score: OS**

![Graph of OS (%)](image1)


**Management recommendations**

- Primary treatment of PTCL-NOS should be within the context of a clinical trial if possible as standard therapy gives disappointing results.
- Outside trial, CHOEP x 6 cycles remains the standard therapy for those patients < 60 yrs with a normal LDH. Added etoposide does not seem to benefit those ≥ 60 or those with raised LDH. Evidence also suggests improved outcomes with subsequent consolidative autologous HSCT in CR1.
- Local XRT should be considered in addition for patients with stage I/II disease.
- Relapsed or refractory disease should be treated with relapse schedule combination chemotherapy and considered for RIC allogeneic or autologous HSCT or novel therapies within a trial setting.
CNS prophylaxis should be considered using the same criteria as for DLBCL.
6. Angioimmunoblastic T-cell lymphoma (AITL)

Notes

- AITL typically presents in older age group with systemic illness, characterized by B symptoms, generalized lymphadenopathy, hepatosplenomegaly, pruritus, and a skin rash, often mimicking an infectious process. Other features include polyarthritis, ascites/effusions, anaemia, eosinophilia, occasionally pancytopenia, polyclonal...
hypergammaglobulinaemia, raised LDH, circulating autoantibodies including a positive direct anti-globulin test (DAT), cold agglutinins, cryoglobulins and circulating immune complexes. Autoimmune phenomena include AIHA (13%), vasculitis, polyarthritis, rheumatoid arthritis and autoimmune thyroid disease. There can be waxing and waning of symptoms, especially if steroids are given prior to diagnosis with the assumption of an underlying inflammatory disorder. 90% of the patients have stage 3 or 4 disease with bone marrow involvement in 60% and clonal T cells are often present in the peripheral blood. AITL has worse prognostic indices compared with other PTCL with 7 yr EFS rates around 23%.

- AITL can be difficult to diagnose and treat because of the presence of both B- and T-cell clones. It shows prominent vascularization by arborizing venules, expansion of CD21+ follicular dendritic cell networks and the malignant T-cell population, which arises from germinal centre follicular helper T cells, expresses CD4, PD1, CD10, BCL6 and CXCL13. An oligoclonal or monoclonal B-cell population due to the expansion of B cells infected with EBV and secondary, usually EBV+, B-cell lymphoma has been described in some patients. Cytogenetic findings (additional X, aberrations short arm of chromosome 1, trisomy 5) have prognostic significance in AITL. Molecular profiling shows a strong microenvironment imprint and overexpression of genes characteristic of normal follicular helper T cells.

**Management recommendations**

- Rarely, AITL spontaneously regresses, but more usually it follows an aggressive course. Occasionally, asymptomatic patients may be observed before initiation of systemic chemotherapy or managed with steroids or other immunosuppressive therapy (eg cyclosporin) alone.

- Patients often die from infectious complications, which can make delivery of aggressive chemotherapy difficult. Combination chemotherapy may be warranted once a diagnosis is made. However, patients have frequent and early relapses or deaths due to infections.

- Patients requiring therapy should be entered into available clinical trials where possible.

- Outside a clinical trial, CHOEP or FC (fludarabine + cyclophosphamide) would be considered as standard therapies.

- Consolidation with allogeneic or autologous HSCT should be considered for patients with chemo-sensitive disease in first remission or after relapse (if not given in CR1). Allogeneic SCT may also be effective in patients with refractory disease.
7. Anaplastic large cell lymphoma (ALCL), ALK+/ALK-

Notes

- The latest WHO Classification recognizes three distinct subtypes of ALCL: primary systemic anaplastic lymphoma kinase (ALK) positive, primary systemic ALK negative (provisional category) and primary cutaneous types (PCALCL), which have differences in immunophenotype, genetics, and clinical behaviour.

- Approximately 60% of systemic ALCLs are ALK positive (ALK-pos) and have a significantly superior survival to ALK-negative (ALK-neg) cases, justifying the separation of these two categories. However, ALK-neg ALCL still has a better prognosis than PTCL-NOS (5-year OS 49% vs. 32%).

- ALK is a receptor tyrosine kinase, the expression of which is usually restricted to the CNS. The chromosome translocation t(2;5)(p23;q25) results in the formation of a fusion gene of nucleophosmin-anaplastic lymphoma kinase (NPM1-ALK) defining the lymphoma entity ALCL ALK positive. The fusion protein contains a constitutively activated ALK kinase resulting in cell proliferation or anti-apoptotic effects. Gene expression profiles have shown distinct molecular signatures for ALK-pos and ALK-neg ALCL. The gene signature of ALK-neg ALCL is also quite different from that of PTCL-NOS. A restricted number of genes may be useful in clinical risk stratification and selection of therapy.

- ALK-pos ALCL occurs at a young age and the majority of patients present with B symptoms (75%) and 75% present with Stage IV disease. ALCL frequently involves both lymph nodes and extranodal sites (50–80%).

- ALK-pos ALCL expresses CD30, t(2;5)/NPM1-ALK translocation, and variants, and clusterin. Most are epithelial membrane antigen (EMA) positive, express cytotoxic markers, lack CD3 and inconsistently express other T-cell associated antigens. However, 90% have TCR gene rearrangements. ALCLs are negative for EBV (EBV-encoded RNA and latent membrane protein 1).

- ALK negative ALCL is morphologically indistinguishable from ALK-pos ALCL but EMA expression is more variable. They express CD30 and 85% have a T-cell phenotype, the remainder being null. Prognosis lies between ALK+ ALCL and PTCL-NOS, with 5-year OS of 49% compared to 19% for PTCL-NOS. Currently, the management is the same as for ALK-pos ALCL but as the outcomes are less good it is recommended that the standard management should become the same as that for PTCL-NOS. Recently a subset of ALK- ALCL with a translocation involving the DUSP22 locus on 6p25.3 has been identified and found to be associated with a favourable prognosis and a 5-year survival rate of 100%. This subset may not derive benefit from intensified upfront treatment strategies such as ASCT.

- During the last decade numerous reports have appeared of primary breast ALCL occurring in association with breast implants. Such tumours
are frequently ALK negative and primarily occur within the fibrous capsule around the implant, within the peri-implant fluid, as a seroma or otherwise adjacent to the implant. A causal link may be present but the absolute risk for an individual patient remains very small. The possible pathogenetic mechanisms remain unknown. Most cases appear to be localized to the breast and follow a more indolent course but cases of systemic involvement with an aggressive course have also been reported. The latter may be associated with disease of the breast parenchyma as opposed to the fibrous capsule or seroma. It is unclear as to the best management strategy for implant associated ALCL and such approaches require individualized care. For patients with localized disease (fibrous capsule or seroma) it appears that removal of the implant and the capsule are sufficient for many but risk factors to identify and best ways to treat the infrequent patients at higher risk for dissemination are unknown. Additional modalities include consideration or local XRT and combination chemotherapy.

Management recommendations

- Primary cutaneous ALCL (PCALCL) (ALK-neg) should be managed with local excision ± radiotherapy. For troublesome multi-focal skin lesions consider MTX or retinoids or IFNα. Combination chemotherapy should be reserved for those patients with systemic disease.

- Patients with limited stage ALK+ ALCL and no adverse prognostic features by IPI should be treated with 3–4 cycles of CHOP or CHOEP chemotherapy and involved field radiotherapy.

- All other patients should receive 6–8 cycles of CHOP or CHOEP chemotherapy.

- ALK-neg ALCL should be treated as for PTCL-NOS.

- At relapse patients should receive platinum-based chemotherapy or an alternative salvage regimen and patients with chemosensitive disease should be considered for autologous or allogeneic transplant.

- Newer treatments in development include 1) brentuximab vedotin, a monoclonal antibody directed against CD30 and linked to a synthetic analogue (MMAE) of the antitubulin agent dolastatin 10. MMAE is released inside the tumour cell which undergoes G2/M phase cell-cycle arrest and apoptosis. and 2) inhibitors targeting ALK such as crizotinib. Access to these therapies may be available in clinical trials.

EXTRANODAL T CELL Lymphomas

8 Extramodal NK/T cell lymphoma, nasal type (ENKTCL)

Notes

- This is a rare aggressive, largely extranodal lymphoma, usually of NK-cell type (CD2+, CD56+, cCD3e+ TCR gene germline), but with recognized T cell phenotypic variants. It is more common in Asia and South America
and almost invariably EBV associated and often presents as localized
disease in and around the nasal structures. This and a poor survival
earned it the historical term 'lethal midline granuloma'.

- The typical patient is an adult male presenting with facial oedema, nasal
obstruction or epistaxis. Initially disease may be limited to mid-facial
destruction. Tumours are often bulky and locally invasive with extension
and invasion into the orbits, sinuses and oral cavity. Dissemination is
frequent, usually to regional nodes and distant extranodal structures such
as skin, testis and gut. Other cases present as widespread extranodal
disease, with or without nasal involvement and these patients are
systemically unwell. Disease occurring outside the nasal cavity is more
aggressive with short survival times and poor response to therapy. An
association with the haemophagocytic syndrome has been reported.

- Tissue biopsies often contain necrotic material making precise diagnosis
difficult and material should be reviewed by expert haemato-pathologists.
EBER-ISH staining is important and EBV viral load in the blood is
prognostic. Other unfavourable prognostic factors include bone or skin
involvement, expression of p19, Ki67 > 50%, elevated C reactive protein
(CRP), anaemia and thrombocytopenia. TCR is not rearranged. MRI is
superior to CT for assessing the extent of local nasal disease and the
presence of invasion. PET can be helpful in demonstrating occult disease
at additional sites. The main distinction between those cases presenting
with localized disease (stage I/II) and those with more advanced stage –
usually with multiple extranodal sites of involvement is clinically important
because of the apparent sensitivity of the tumour to radiation and the
relative insensitivity to chemotherapy. Localized disease is thus quite
curable with radiotherapy but disseminated disease does poorly.

- The IPI is valid only in the sense that a low score is seen in localized
disease and a high score in the disseminated cases, which predicts
curability with radiation. Even the low-IPI cases have a poor survival
compared to other aggressive lymphomas; however, Lee et al (Journal of
Clinical Oncology, 2006 24, 612–618) have developed a prognostic model
which includes four risk factors: B symptoms, advanced stage IV,
elevated LDH and involvement of regional lymph nodes. The 5-year OS
according to number of risk factors was 81% for 0, 64% for 1, 34% for 2
and 7% for those with 3 or 4.

Management recommendations (see NCCN guidelines for details)

- Patients with localized stage 1 nasal disease without risk factors should
receive radiation with XRT 50–55 Gy alone;

or be considered for concurrent chemo-irradiation; Regimens include 50
Gy XRT and 3 courses of DeVIC (dexamethasone, etoposide, ifosfamide
and carboplatin); or 40-50Gy XRT followed by 3 cycles of VIPD
(etoposide, ifosfamide, cisplatin and dexamethasone).

Stage 1 patients require post RT evaluation (MRI/nasal endoscopy and
biopsy and EBV viral load). If CR observe. If PR/refractory disease
consider salvage chemotherapy followed by allogeneic stem cell
transplantation (SCT).
• Patients with stage II disease or stage I with risk factors could be considered for clinical trial or concurrent or sequential irradiation (SMILE or VIPD followed by XRT 40-50.4Gy).

• Patients with stage IV nasal disease or extra-nasal disease should be considered for clinical trial or concurrent chemo-irradiation or pegylated asparaginase based combination chemotherapy regimen +/- XRT. The latter regimens include Pegasparaginase/MTX/Dex – reported as second line regimen and SMILE (steroid (dexamethasone) /MTX/ifosfamide /pegasparaginase and etoposide).

• Patients with more advanced disease and PR / CR following first line therapy should be considered for consolidative allogeneic SCT.

• Patients with refractory disease post first line therapy should be considered for salvage chemotherapy or best supportive care.

9 Enteropathy-associated T-cell lymphoma (EATL)

Notes
• This is a rare aggressive large cell tumour of the small bowel, which is strongly associated with HLA DQ 2 or 8 (95%) and coeliac disease, either overt or silent. It may be the presenting feature in adults of previously undiagnosed coeliac disease. In 10–20% of cases the histology is monomorphic (type II EATL) and may occur sporadically, without risk factors for coeliac disease.

• The typical patient is an older (median age 57 years) male presenting with diarrhoea and abdominal pain; if coeliac progressing with worsening malabsorption and finally terminating in overt bowel lymphoma with ulceration, obstruction or perforation. The sites of involvement are usually jejunum or ileum – often with multiple, ulcerative lesions.

• The outcome is poor, partly due to the biology of the disease and partly because of the poor PS of patients in the setting of malabsorption and malnutrition.

• Diagnosis and staging use the same investigations and techniques as for PTCL-NOS (see above). In addition, it is important to liaise with an experienced gastroenterologist to assist with biopsy, staging and follow up and to manage nutritional problems.

• Cells are typically CD3+, CD7+, CD4-, CD5-, CD8/56 +/-, CD103+, CD30+/-, TIA1/GRB/Perf +. Type II EATL has distinct immunophenotype being CD3+, CD8+, CD56+, TCRβ+.

• Assigning a conventional IPI score is of limited value as there is no good prognostic group and most cases are stage I–II E.

Management recommendations

• Trial or experimental therapy should be considered if available eg current UK NCRI study.

• CHOP-like therapy, with or without an up-front autograft remains a common approach outside a trial but evidence of efficacy is lacking and
adoption of a more intensive approach, such as the NCRI/SNLG protocol (CHOP for one cycle followed by IVE (ifosfamide, etoposide, epirubicin) for three cycles alternating with intermediate-dose methotrexate and up-front autologous transplantation) is a reasonable option in fitter patients.

- Nutrition is a major issue in managing these patients and dietetic/gastroenterology advice is essential at all stages of treatment and follow-up.

**Enteropathy-Associated T-Cell Lymphoma: The Newcastle Regimen**

- Newcastle regimen: CHOP x 1, followed by IVE (ifosfamide, etoposide, epirubicin, methotrexate), followed by ASCT

![Graph showing comparison between Newcastle and Conventional chemotherapy for PFS and OS](image)


*Anthracycline based

10. **Hepatosplenic T-cell lymphoma (HSTCL)**

**Notes**

- Median age is 34 years. Systemic, extranodal disease involving the liver, spleen and bone marrow. Lymphadenopathy is a rare. Marrow involvement causes cytopenias, thrombocytopenia being the most common. Can be associated with severe immunosuppression, eg after solid organ transplant.
- Most cases show a characteristic phenotype (negative for CD5,7,4,8,GRB/perforin; CD3+, CD56+, TIA1+), expression of the γδ T-cell receptor, and have an isochromosome 7q abnormality. A variant expressing the αβ T-cell receptor is also described.
- The outlook is very poor, with only occasional survivors reported in the few, small series in the literature.

**Management recommendations**

- Trial or experimental therapy should be considered if available
- Conventional chemotherapy approaches as for PTCL-NOS are the default and there are some survivors reported in the literature.
- Allogeneic SCT could be considered if patient receives CR.
MATURE T-CELL NEOPLASMS WITH PREDOMINANT LEUKAEMIC PRESENTATION

11. Adult T-cell leukaemia/lymphoma (ATLL)

Notes
- Caused by retrovirus, HTLV-I, which is endemic in Japan, the Caribbean, Africa, South America and parts of the south-eastern USA. Very rare in NZ.
- HTLV-I infection affects 15–20 million individuals worldwide although 95% of these are likely to remain asymptomatic carriers, with an estimated lifetime risk of developing ATLL of 1–5%.
- The development of ATLL from HTLV-I infected CD4+ regulatory T lymphocytes is likely due to the effects of the Tax viral transactivator protein. High incidence of TP53 mutations in advanced cases.
- Classified into four clinical subtypes by the Japanese Clinical Oncology Group (JCOG). Various adverse prognostic factors and scoring systems have also been proposed. These include high LDH, high WBC, hypercalcemia, age >40 years, more than three involved lesions, poor PS, thrombocytopenia, eosinophilia, bone marrow involvement, CCR4 expression and TP53 mutation. The poor prognosis of the leukemic and lymphoma subtypes reflects a combination of lymphoma resistance to therapy, immunosuppressed status, age and poor performance status.

<table>
<thead>
<tr>
<th>ATLL Type</th>
<th>Relative % incidence</th>
<th>Clinical Features</th>
<th>Prognosis 4 yr OS</th>
<th>M S (Mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Leukaemic</td>
<td>57</td>
<td>Rapidly ↑ WBC, ↑ calcium, Bone, CNS, GIT involvement</td>
<td>5%</td>
<td>6.2</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>19</td>
<td>Lymph &lt; 4.0; Gen LN, Splenomegaly, GIT</td>
<td>5.7%</td>
<td>10.2</td>
</tr>
<tr>
<td>Chronic</td>
<td>19</td>
<td>Lymphocytosis, LN, Hepatosplenomegaly, Skin, lung.</td>
<td>26.9%</td>
<td>24.3</td>
</tr>
<tr>
<td>Smouldering</td>
<td>5</td>
<td>Normal WBC; Skin and lung; indolent course</td>
<td>62.8%</td>
<td>NYR</td>
</tr>
</tbody>
</table>

- Key diagnostic points: Lymphocytes have flower shaped morphology; PB Cells > 4.0 x 10^9/L in acute/chronic subtypes. Cells CD4+, CD25+, CD7 is usually negative (nb positive in T-PLL). Other positive markers include CD3 (dim), CD2, CD5, CD45RO, CD29, TCRαβ and HLA-DR. HTLV1 Elisa
positive; Use western blot/ HTLV-1 PCR in equivocal cases. Tissue biopsy as required when PB not involved. sIL-2R good marker of tumour burden.

Management Recommendations

- Consult latest literature/JCOG for advice on patient management. Mortality from ATLL appears to be declining.
- Enroll on clinical trial if possible
- Patients are highly immunosuppressed. Exclude co-infection with Strongyloides prior to commencing therapy. High risk for PCP, invasive fungal infection and CMV reactivation. Appropriate antimicrobial prophylaxis (co-trimoxazole and acyclovir) and /or preemptive monitoring is required during therapy.

Smouldering and chronic types

- Watch and wait.
- Skin directed therapies as clinically indicated (as per MF).
- Zidovudine (AZT) + IFN-a ± MoAbs may be considered in the context of a clinical trial.

Leukaemia/ lymphoma types.

- Optimal therapy not yet established
- Consider induction with CHOP or alternative multi-agent regimens plus G-CSF. Other options include CHOEP/hyper-CVAD/EPOCH and VCAP-AMP-VECP.
- Concurrent AZT + IFN-a.
- Allo HSCT in first CR for eligible patients. or AZT + IFN-a maintenance + MoAbs or consolidation with novel agents e.g. Arsenic trioxide, IFN-a; proteasome inhibitor in clinical trials.
- CNS prophylaxis should be considered, using the same criteria as for diffuse large B-cell NHL.

12. T-cell prolymphocytic leukemia (T-PLL)

Notes

- T-PLL is an aggressive malignancy presenting with splenomegaly, lymphadenopathy and a high white blood cell (WBC) count, which is in excess of 100 · 10^9/l in 50% of cases.
- Some patients may present with an indolent phase which inevitably progresses.
- Overall prognosis is poor with a median OS of approximately 7 months in historic series of patients treated with conventional chemotherapy. In recent years the survival of patients with T-PLL has improved following the introduction of the newer agents, pentostatin and alemtuzumab.
- The circulating prolymphocytes have a distinctive morphology and express mature T-cell markers (terminal deoxynucleotidyl transferase-
negative, CD2 positive, CD3 weakly positive or negative, CD5 positive and strong CD7 positive) with variable expression of the CD4 and CD8 antigens.

- Conventional cytogenetic analysis usually demonstrates complex abnormalities. Inversion 14 is seen in 75% of cases and more than half of the cases have abnormalities of chromosome 8. Two oncogenes, TCL1A and MTCP1, are often over expressed. The ATM gene on 11q23 is also frequently involved in T-PLL and may be important in the pathogenesis.

Management recommendations (see guidelines documents for treatment references)

- Clinical trial preferred
- Consider prophylaxis for tumour lysis
- Note CMV reactivation/other opportunistic infections with alemtuzumab containing regimens. For acyclovir and cotrimoxazole prophylaxis and pre-emptive monitoring for CMV.
- IV alemtuzumab as single agent, 30mg x 3/wk for 12 weeks
- FCM x 4, followed by alemtuzumab 1-3 months
- Alemtuzumab and pentostatin
- Consider RIC allogeneic SCT in CR/PR1

13. T-cell large granular lymphocytic leukaemia (T-LGL)

Notes

- T-LGL leukaemia is characterized by a persistent (>6 months) increase in peripheral blood (PB) LGLs. Splenomegaly is seen in about two-thirds of patients but lymph node enlargement is rare. The lymphocytosis is usually between 2 and 20 \( \cdot \) 10^9/l.
- More common in patients with auto-immune disorders, particularly rheumatoid arthritis.
- T-LGL leukaemias typically have an indolent clinical behaviour with a median survival of >10 years. Rare cases follow a more aggressive course.
- Cytopenias are the most common indication for treatment. Eighty-five percent of patients develop neutropenia at some time during the disease course and is severe (<0.5 \( \cdot \) 10^9/l) in 50%.
- Most LGL leukaemias (80–90%) are CD3 positive with co-expression of TCR \( \alpha \beta \), CD8, CD16 and CD57 and with CD56 being negative. Uncommon variants include CD4+ cases and those with TCR \( \gamma \delta \). The aggressive variants may be CD56+/CD57-.
- Patients do not require therapy unless symptomatic from cytopenias or other complications.
- The majority of cases will follow an indolent course and aggressive chemotherapy is not indicated.
- The decision to treat is based on: significant symptomatic anaemia (<90 g/l) and/or the need for transfusion; severe neutropenia (<0.5 * 10^9/l) associated with infection; severe thrombocytopenia (<50 *10^9/l); or any combination of these.
- Oral cyclosporin or weekly oral low dose methotrexate (10 mg/m² per week) are effective in more than 75% of cases.
- Responses may be enhanced by the use of growth factors (erythropoietin and/or G-CSF).
- Second line treatments include purine analogues (cladribine, pentostatin), cyclophosphamide and alemtuzumab.

14. **Chronic lymphoproliferative disorder of NK-cells** (CLPD-NK)

**Notes**
- Provisional entity; defined by NK cells > 2*10^9/L for 6 months. No regional or EBV association; Difficulty discriminating between reactive vs clonal NK populations. Features of clinical disease (B symptoms and infiltration of liver, spleen and bone marrow) and cytogenetic abnormality (most common del(6q)) support diagnosis of clonal disease.
- Cells have NK cell phenotype eg CD2 positive, CD3 negative, CD4 negative, CD8 negative, CD16 positive, CD56 positive, CD57 negative; TCR PCR negative.

**Management recommendations**
- As for T-LGL

15 **Aggressive NK cell leukaemia**

**Notes**
- Rare, associated with EBV infection, with strong regional incidence association with Asian countries.
- Occurs in young adults; Acute presentation with B symptoms (particularly fever), jaundice, lymphadenopathy, hepato-splenomegaly, circulating leukaemic cells and cytopenias. Skin involvement is rare. Disseminated intravascular coagulation (DIC), haemophagocytic syndrome, liver dysfunction and multi-organ failure may occur. Serum LDH is usually very high.
- NK cells of slightly immature appearance, often with nucleoli, may be seen in the peripheral blood and bone marrow. These neoplastic cells are CD2; sCD3-, CD3e+, CD56+, CD57-, CD16+ (75%) with germline TCR genes. High levels of FAS ligand can be found in the serum. In most cases there is clonal integration of EBV. The commonest cytogenetic abnormalities are del (6q), del (11q) and del (17p).
Typical fulminant course with fatal outcome with survival of 2 months

**Management recommendations**
- Innovative treatments required, in clinical trials
- Typically ALL type treatments used with CNS prophylaxis.
- Allogeneic SCT should be considered if patient achieves CR.

**PRIMARY CUTANEOUS LOCALISATION (NON-ANAPLASTIC MORPHOLOGY)**

16 **Mycosis fungoides (MF) and Sézary syndrome (SS)**

**Notes**
- MF is an indolent extranodal lymphoma of mature T cells with primary cutaneous involvement which accounts for 50-70% of cutaneous T cell lymphoma (CTCL). It has the potential to progress to cutaneous tumours and generalised erythroderma and metastasize to lymph nodes, blood and visceral organs with a much poorer prognosis. SS is currently defined by the ISCL as a distinctive, erythrodermic CTCL with evidence of leukemic involvement, accounting for only 1-3% of CTCL cases. The WHO/EORTC considers SS to be a separate entity from cases that otherwise meet the criteria for SS but have been preceded by clinically typical MF. Such latter cases have been designated as “SS preceded by MF” and also as “secondary” SS. Dermatologists are usually involved with patients with early stage disease, whereas haematologists are often involved with patients with end stage disease where combination chemotherapy regimens are under consideration.

![Graph showing disease-specific survival of mycosis fungoides/Sézary syndrome](image)

Disease-specific survival of 525 patients with mycosis fungoides/Sézary syndrome according to TNM stage. Patients with early-stage disease have excellent disease-specific survival, with most

- Patients initially present with localised skin involvement with patches or plaque disease. Assessment includes skin examination for extent of disease (ie % body surface area), the type of skin lesion (patch/plaque/tumour/erythroderma), biopsy of suspicious skin sites with appropriate immunohistochemical studies, examination for lymphadenopathy and organomegaly (with possible CT) and possible assessment of blood involvement by morphology, flow cytometry and PCR studies for rearranged TCR genes. Biopsy of suspicious LN (≥ 1.5cm) with TCR PCR studies is recommended but bone marrow biopsy is not required for routine staging but may be helpful in those with B2 involvement or unexplained cytopenias. The classical immunophenotype of MF is CD3+, CD2+, CD5+, CD4+, CD7-, CD8-, CD26- with positivity for CCR4, CD45RO and CLA. If large cell transformation is present additional staining for CD30 is recommended. Significant blood involvement (B2) is defined as the presence of rearranged TCR genes in the peripheral blood (clonally related to neoplastic T cells in the skin) and either an absolute Sézary cell count of 1 x 10E9/L or increased CD4+ cells with an abnormal phenotype (CD4+/CD7- 40% or more or CD4+/CD26- 30% or more).

- The International Society for Cutaneous Lymphomas and the EORTC have recommended revisions to the initial TNM staging system developed by the Mycosis Fungoides Co-operative Group. This is based on assessment of skin, nodal, visceral and blood involvement and is reproduced below.

**ISCL/EORTC revision to the classification of MF and SS**

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* **Patch** indicates any size lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.

* **Plaque** indicates any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or
poikiderma should be noted. Histologic features such as folliculotropism or large-cell transformation (>25 percent large cells), CD30+ or CD30-, and clinical features such as ulceration are important to document.

\*Tumour indicates at least one 1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histologic evidence of large-cell transformation has occurred. Phenotyping for CD30 is encouraged.

\*Abnormal lymph node(s) indicates any lymph node that on physical examination is firm, irregular, clustered, fixed, or 1.5 cm or larger in diameter or on imaging is >1.5 cm in the long axis or >1 cm in the short axis. Node groups examined on physical examination include cervical, supraclavicular, epitrochlear, axillary, and inguinal.

\*A T-cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene.

\*¥For viscera, spleen and liver may be diagnosed by imaging criteria alone.

\*‡The clone in the blood should match that of the skin. The relevance of an isolated clone in the blood or a clone in the blood that does not match the clone in the skin remains to be determined.
Management recommendations (see NCCN guidelines).

- Due to the rarity of condition and the need for an individualised approach referral to and/or discussion with a multidisciplinary specialised centre is recommended (eg Peter MacCallum Cancer Centre, Melbourne).

- The initial treatment of patients with patch/plaque disease consists of skin-directed therapies (SDT; localised or generalised, vide infra) with the addition of systemic biologic or chemotherapy for patients with refractory/progressive disease. Thicker lesions (i.e. tumours) are less likely to respond to SDT. The early use of therapy does not impact on survival and a non-aggressive approach is warranted, aimed at controlling skin lesions whilst minimising morbidity.

Skin Directed Therapies for localised/limited skin involvement (eg stage IA-IIIA)

- Potent or superpotent topical corticosteroids (e.g. clobetasol propionate ointment) is generally first-line treatment; (note: long term use of >50 gm/week of super potent topical corticosteroid maybe associated with skin atrophy and/or systemic absorption, particularly if used under occlusion). Applied once daily at night.

- Intralesional corticosteroids (e.g. triamcinolone 10-40 mg/ml) may be effective for localised persistent plaques/tumours. Repeated as required every 2-3 months.

- Topical retinoids: bexarotene 1% gel (currently not available in NZ) can be effective in early stage, localised disease. Topical retinoids available in New Zealand include tretinoin, isotretinoin and adapalene. Applied once daily at night.

- Phototherapy x3/week (narrow band ultraviolet light B (nbUVB) for patch/thin plaques; psoralen + ultraviolet light A (PUVA) for thicker plaques). Suitable for more widespread disease; (note: acute side effects of PUVA include nausea from oral psoralens (avoided with cream-PUVA, bath-PUVA or nbUVB), pruritus and photosensitivity.

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Cumulative PUVA dose (but not nbUVB) associated with acceleration of actinic skin damage and increased risk of UV associated skin neoplasms; therefore may not be appropriate in patients with a history of extensive basal cell and squamous cell carcinomas or melanoma.

- Photodynamic therapy (PDT) involves irradiation (usually within red spectrum) of tumour cells pre treated with photosensitisers (e.g. 5-aminolevulinic acid or methyl aminolevulinic acid). PDT can be useful in limited disease. Usually two treatments at 1-2 week intervals.

- Topical chemotherapy (0.1-0.2% mechlorethamine (nitrogen mustard) or carmustine (1,3-bis[2-chloroethyl]-1-nitrosourea/BCNU)). Apply daily until lesions clear. Maintenance treatment for 1-2 months after. May take over 6 months to achieve skin clearance. Relatively easy to use but some logistical formulation/application issues; risk of hypersensitivity (reduced by ointment formulation) and secondary epithelial malignancy with long term use. Risk of bone marrow suppression with carmustine.

- Topical imiquimod (5%) is a toll-like receptor-7 agonist and stimulates the production of IFN. Numerous case reports of benefit for localised lesions, including tumours. Applied x3-5/week for 6-12 weeks).

- Local irradiation (12-36Gy). Cutaneous lymphomas are highly radiosensitive; The likelihood of achieving a CR and the durability of response decreases with increasing stage of disease. Also consider Grenz rays.

- Total skin electron beam therapy (TSEBT) 12-36Gy (available at Waikato hospital). Reserved for those with severe skin symptoms or generalised thick plaque or tumour disease or poor response to other therapies. A 30-36 Gy course is delivered over a 9-10 wk period. It is common practise to follow TSEBT with systemic adjuvant therapy to maintain response.

- Systemic therapies are preferred over traditional chemotherapy for patients who do not respond to initial skin directed therapies. It is generally deferred until a patient has failed multiple treatments with local and skin directed therapy. Skin directed therapy can be used as adjuvant treatment to help control skin related symptoms. Single agent methotrexate is often included in this category of treatment. Options include:
  - Low dose methotrexate (15-20 mg/week).
  - Extracorporeal photopheresis (ECP), (note: currently not available in NZ). Particularly useful for patients with blood involvement (e.g. B1 or B2).
  - Systemic oral retinoids/rexinoids (isotretinoin (0.5-2.0 mg/kg/day), acitretin (0.25-0.75 mg/kg/day), all trans retinoic acid (tretinoin/ATRA), and bexarotene (300mg/m²/day); monitoring for side effects is required; bexarotene is particularly associated with hypertriglyceridaemia and hypothyroidism). All are potent teratogens.
• Interferons (IFN alpha nb tolerance/compliance issues; IFN-gamma)
• Histone deacetylase inhibitors (HDACi); eg vorinostat
• Combination approaches of above modalities (eg Retinoid + IFN, ECP + retinoid and/or IFN, MTX with PUVA.)
• Denileukin diftitox (problematic re cost/administration/side effects/tumour CD25+; usually considered after failure of other options)

• Conventional cytotoxic systemic chemotherapy or participation in a clinical trial is generally recommended as a primary treatment for patients with advanced disease or large cell transformation, as second line therapy for early stage disease refractory to skin directed therapies and systemic biologic therapies and for patients with subsequent relapsed or progressive disease. Skin directed therapy can be used as adjuvant treatment to help control skin related symptoms. Currently there is no definitive treatment for advanced disease that can produce reliable durable remissions or curative outcomes apart from, possibly, allogeneic stem cell transplantation. Single agents are often preferred over combination regimens (except when rapid response needed) on account of similar response rates/duration but lower toxicity/infection risks. Options include:
  • Gemcitabine
  • Liposomal doxorubicin
  • HDAC inhibitors
  • Pentostatin
  • Methotrexate (> 100mg q weekly) or (other standard agents such as Cyclophosphamide/chlorambucil or etoposide)
  • Low / standard dose pralatraxate
  • Alemtuzumab. Lower doses administered subcutaneously have shown a lower incidence of infectious complications
  • Miscellaneous other single agent/combination chemotherapy regimens
  • Allogeneic SCT. This therapy has been performed on small numbers of highly selected patients and long term survivors have been reported. Such patients require careful individual evaluation and selection and comparison between transplant and non-transplant options that may be available to them. It appears that the best results may be associated with those patients that have chemosensitive disease prior to SCT; have good performance status, have an HLA-identical sibling donor and undergo reduced intensity conditioning therapy. Therefore patients should be referred for consideration of SCT before they have become refractory with declining performance status.
Supportive care for patients with MF/SS. This is an important but often neglected aspect of patient care. Pruritus can be a very distressing patient symptom.

- **Pruritus**: local and generalised pruritus should be distinguished and correlation between sites of disease and pruritus should be noted. Consultation with dermatology service is advised. A broad array of topical and systemic approaches can be used (see NCCN guidelines).

**Infection treatment and prophylaxis.** Patients with MF/SS may develop immune collapse (due to decrease in immunocompetent T cells) and are often colonised with *Staphylococcus aureus*. Local or generalised skin infection is often misdiagnosed as or is a driver of progressive MF/SS. Clinicians need to be alert to this possibility and have a low threshold for culture and treatment as required. Local bleach baths or soaks may be appropriate for localised areas but otherwise treatments may include intranasal vaseline and antibiotic therapy with agents such as oral flucloxacillin, cotrimoxazole or doxycycline or iv vancomycin if there is no improvement or associated bacteraemia. In addition ulcerated and necrotic tumours may be associated with local gram negative sepsis and bacteraemia. Patients receiving purine analogues require HSV and PCP prophylaxis and are at risk of invasive fungal infections and patients receiving alemtuzumab are at additional, particular risk for CMV reactivation.

17 Primary cutaneous CD30+ T-cell lymphoproliferative disorders

**Primary cutaneous anaplastic large cell lymphoma (PC ALCL)**

**Notes**

- Typically seen in older men as a solitary asymptomatic cutaneous or subcutaneous reddish nodule. Nodal disease is seen in about 10% of cases and mainly involves regional lymph nodes. In contrast to systemic ALK-neg ALCL this has a good prognosis. The course is indolent, with occasional spontaneous remissions but frequent relapses, generally confined to the skin. A review of 146 cases showed a 10-year survival of 95%. Multi-focal skin lesions, especially those sited on the leg, appear to have a poorer prognosis.

- Histology shows diffuse, non-epidermotrophic infiltrates with cohesive sheets of large CD30 positive tumour cells, which show am activated Cd4+ T cell phenotype with variable loss of CD2, CD5 or CD3 and frequent expression of cytotoxic proteins, granzyme B, perforin and TAl1. Most express CLA but not EMA, ALK or CD15. TCR genes are usually rearranged. Less commonly the cells may have a non-anaplastic appearance.

**Management recommendations**

- Treatment is directed at local control with excision and/or radiotherapy and patients may be successfully re-treated.
- Thin lesions may respond initially to clobetasol propionate ointment under occlusion or intralesional triamcinolone.
For troublesome multi-focal skin lesions low dose MTX (15-20 mg once a week) or systemic retinoids (acitretin 0.25-0.5 mg/kg/day, isotretinoin 0.5-2 mg/kg/day) or IFNα (initial dose 1-3 MU x3/week) can be considered. Aggressive treatment should be avoided although chemotherapy may be indicated if there is systemic disease.

**Lymphomatoid papulosis (LyP)**

**Notes**
- Chronic recurring self-healing skin disorder affecting trunk and extremities. Lesions may be papular, papulonecrotic and/or nodular at different stages of development. Individual skin lesions disappear after 3-12 weeks and may leave behind superficial scars. Can be associated with MF, cutaneous ALCL or Hodgkin lymphoma.
- Histology is variable, partly relating to stage of the lesion. Three histological subtypes are described. Types A and C include large anaplastic cells that are CD30+. TCR genes are rearranged in 60% of cases.

**Management recommendations**
- Reassurance and observation for limited disease.
- Topical (clobetasol propionate ointment) or intralesional triamcinolone may be useful in limited disease.
- Surgical excision or local XRT may be appropriate for single large lesions (> 2cm).
- Low dose MTX (15-20 mg x1/week) or phototherapy (either nbUVB or PUVA x3/week) for patients with numerous, disseminated, or stigmatizing lesions. Associated with more rapid healing. Risk of recurrence with requirement for maintenance. Note risks of long term toxicities with PUVA.
- Avoid multi-agent chemotherapy
- Long term follow up is required In view of association with other cutaneous lymphomas. In larger lesions or if any lesions do not show evidence of spontaneous regression after several months, progression to PCALCL or Mycosis fungoides (MF) should be considered.

18 **Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)**

**Notes**
- Distinction should be made between the αβ type and the γδ type which is now included in the *Primary cutaneous gamma-delta T-cell lymphoma* category.
- Presentation is typically with multiple, indurated, subcutaneous nodules up to a few centimetres in size and ulceration is uncommon. Lesions maybe solitary. Some cases have an indolent prodrome with recurring and self-healing lesions. The lesions may show overlapping features with lupus profundus panniculitis. The distribution is mainly extremities and trunk. Lymphadenopathy and systemic involvement can occur in advanced disease but are relatively unusual at diagnosis. Systemic symptoms such
as fever, fatigue and weight loss may be present in >50%. Laboratory abnormalities, including cytopenias and abnormal liver function tests are common. The presence of haemophagocytic syndrome (15-20%) is associated with a much poorer prognosis. There is

- Biopsy shows involvement of fat and subcutaneous tissue with sparing of the overlying skin layers. Cells are TCRαβ+ and CD8+, express the cytotoxic markers granzyme B, perforin and TIA1, express βF1 and are negative for CD56 and EBV is absent.

- It is important to stage the patient fully as localized presentations may have a relatively good prognosis.

**Management recommendations**

- Optimal strategies are uncertain. Initial observation may be appropriate or more conservative immunosuppressive regimens such as cyclosporine and prednisone may be effective. Such cases, who follow a more indolent course, may be more common in Maori and other polynesians. Local XRT may also be used for very localized disease.

- Conventional chemotherapy and consolidation ASCT in CR1 may also be indicated in patients with more advanced features or who progress after initial single agent immunosuppressive therapy.

### 19 Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (AECTCL)*

**Notes**

- This provisional entity is characterised by epidermotropism and aggressive clinical behaviour. Tumours show central ulceration and necrosis.

- Cells are CD3+, TCRαβ+ and CD8+, express the cytotoxic markers granzyme B, perforin and TIA1, express βF1 and are negative for EBV.

**Management recommendations**

- Optimal strategies are unknown. As prognosis is poor with conventional chemotherapy. Undertake literature review and seek expert advice.

### 20 Primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL)

- Patients present with varying generalised skin lesions, preferentially affecting the extremities. Haemophagocytic syndrome can occur.

- Three major histological patterns occur, epidermotrophic, dermal and subcutaneous. Cells are βF1 negative, CD3+, TCRδ+ and express CD56
and the cytotoxic markers granzyme B, perforin and TIA1, EBV is negative.

**Management recommendations**

- Optimal strategies are unknown. Cases are resistant to conventional combination chemotherapy and irradiation. Undertake literature review and seek expert advice.

21 **Primary cutaneous small/medium CD4+ T-cell lymphoma (SMPTCL)**

- This provisional entity is a cutaneous T cell lymphoma characterised by a predominance of small to medium sized CD4+ pleomorphic T cells without evidence of patches and plaques typical of mycosis fungoides. A majority of patients present with a solitary skin lesion, most commonly on the face, neck or trunk.

- Dense diffuse or nodular infiltrates within the dermis. Cells are TCR PCR+(60% cases), CD3+, CD4+, CD8- and CD30-, sometimes with loss of pan-T cell markers. Cytotoxic markers and EBV are negative. Admixed polyclonal plasma cells and B cells may be present making distinction from a reactive process difficult in some cases. In view of the benign clinical course other terms for this entity have included “T cell pseudolymphoma” and a more recent recommendation “cutaneous nodular proliferation of pleomorphic T lymphocytes of undetermined significance”.

**Management recommendations**

- Surgical excision or XRT for localised lesions. Excellent prognosis.

- Patients with multiple lesions or large tumours may have a more aggressive course and should be considered for chemotherapy following literature review and expert advice.

22 **Blastic plasmacytoid dendritic cell neoplasm (BPDCN)**

- Blastic plasmacytoid dendritic cell neoplasm (BPDCN), formerly known as CD4+/CD56+ haematodermic neoplasm, is a rare hematopoietic malignancy derived from the precursors of plasmacytoid dendritic cells. Although not a T cell neoplasm it is included in view of its typical cutaneous presentation.

- It is a clinically aggressive tumour which usually presents in elderly patients with asymptomatic solitary or multiple skin lesions that can be nodules, plaques or bruise like areas with rapid progression to LN and BM/PB. The overall prognosis for BPDCN is remarkably poor. Most patients show an initial response to acute leukemia–like chemotherapy, but relapses with subsequent drug resistance occur in virtually all patients, resulting in a median overall survival of only 12-14 months.

- Cells are positive for CD4 and CD56, HLA-DR, coupled with at least one plasmacytoid dendritic cell-associated antigen among CD123, TCL1,
CD2AP and BDCA2/CD303, MxA in the absence of any of the stem cell (CD34 and CD117) or lineage-specific markers for B cells (CD20, CD79a), T cells (CD3), myeloid cells (myeloperoxidase) and monocytes (CD11c, CD163, lysozyme). EBV is negative. tdT is positive in 1/3 of cases. An extensive range of genetic abnormalities have been identified by cytogenetics, CGH and GEP.

Management recommendations

- Consider acute leukaemia induction therapy (? ALL better than AML).
- High-dose therapy followed by allo-SCT from related or unrelated donors can provide durable remission even in elderly patients with BPDCN, especially for those in CR at the time of SCT.


12. W N Patton, May 2013