Guidelines for the Management of Mature T-cell and NK-cell Neoplasms (Excluding cutaneous T-cell Lymphoma) Updated August 2013

British Committee for Standards in Haematology

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Introduction

The mature or peripheral T-cell neoplasms are a biologically and clinically heterogeneous group of rare disorders that result from clonal proliferation of mature post-thymic lymphocytes. Natural killer (NK) cells are closely related to T cells and neoplasms derived from these are therefore considered within the same group. The World Health Organisation (WHO) classification of haemopoietic malignancies has divided this group of disorders into those with predominantly leukaemic (disseminated), nodal, extra-nodal or cutaneous presentation (Harris *et al*, 1999, Swerdlow *et al*, 2008) (Table 1). Within the WHO classification these malignancies are differentiated on the basis not only of clinical features but also of morphology, immunophenotype and genetics.

The mature T-cell and NK-cell neoplasms usually affect adults and most of the entities described are more commonly reported in males than in females. The median age at diagnosis for the group as a whole is 61 years with a range of 17-90 years. Although some, such as T-cell large granulocyte leukaemia (T-LGL) and early stage mycosis fungoides (MF) may follow a relatively benign protracted course others have an aggressive clinical behaviour and poor prognosis. Excluding anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and indolent MF, which have a good outcome (Gascoyne et al, 1999), 5 year survival for other nodal and extranodal T-cell lymphomas is about 30%. Most patients present with unfavourable international prognostic index (IPI) scores (>3) and poor performance status (PS). The similarity between progression free survival (PFS) and overall survival (OS) is an indication of the poor response to second line therapies.

The rarity of these diseases and the lack of randomised trials mean that there is no consensus about optimal therapy for T- and NK-cell neoplasms and recommendations are therefore based on small case series, phase II trials and expert opinion.

Methods

This guideline is an update of the 2010 guideline compiled by a T-cell Working Group on behalf of the British Committee for Standards in Haematology (BCSH). The guideline group was selected to be representative of UK-based medical experts and patient representatives and included 5 UK Haematologists, two with a background in stem cell transplantation, one medical oncologist and a dermatologist. Advice was also sought from experts in radiation oncology and patient advisory groups.

Because of the wide variability within this group of diseases, recommendations for therapy are based on individual subtypes where this is possible. We have therefore separated the clinical recommendations into three parts; leukaemic, nodal, and extranodal sub-categories. Management guidelines for cutaneous T-cell lymphoma (CTCL) will be covered in a separate document.

The production of the guidelines involved the following steps:

- Review of key literature in English, including MedLine, EMBASE and Internet searches up to **December** 2012.

- Consultation with representatives of other specialities including clinical oncology
- Assessment of the level of evidence and grade of recommendation were based on the literature review and a consensus of expert opinion. The GRADE system has been used to quote the levels and grades of evidence (see table 2)
- Adherence to the BCSH procedure for guidelines development (http://www.bcshguidelines.com/process1.asp)

The objective of this guideline is to provide healthcare professionals with clear guidance on the management of patients with mature T-cell and NK-cell neoplasms. It should be recognised that limited evidence was available. and that no grade A recommendations could be made because of lack of data from randomised controlled trials. Historically, most information regarding management of T-cell lymphomas has been derived retrospectively from studies conducted predominately in B-cell non-Hodgkin lymphoma (NHL) which included small numbers of peripheral T-cell lymphomas (PTCL) which were of differing histological types, further confusing interpretation. It is only more recently, following the advent of B-cell directed antibody therapy that T-cell lymphomas have been singled out for separate clinical studies. As yet these are largely phase II studies or small case series. The guidance may not be appropriate to all patients in this disease group and in all cases individual patient circumstances may dictate an alternative approach.

Following some general comments regarding incidence, diagnosis, staging and prognosis applicable to all disease subtypes there will be a more detailed discussion in relation to the specific entities as defined in the WHO classification.

Summary of specific entitities

I Mature T-cell Leukaemias

1. **T-Prolymphocytic Leukaemia (T-PLL)**
2. **T-Large Granular Lymphocytic Leukaemia (T-LGL)**
3. **Chronic Lymphoproliferative disease of NK cells (CLPD-NK)**
4. **Aggressive NK-cell Leukaemia**
5. **Adult T-cell Leukaemia lymphoma (ATL)**

II. Nodal PTCL

6. **Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)**
7. **Angio-immunoblastic T cell lymphoma**
8. **Anaplastic Large cell lymphoma- ALCL**

III. Extranodal PTCL

9. **Extranodal NK/T-cell lymphoma, nasal type**
10. **Enteropathy-Associated T-cell lymphoma (EATL)**
11. **Hepatosplenic T-cell lymphoma**
12. **Subcutaneous panniculitis-like T-cell lymphoma SPTCL**

Incidence and epidemiology

Together, the mature T- and NK-cell neoplasms account for approximately 10-12% of all lymphoid malignancies. SEER data (1992-2001) in the US reports an incidence for T/NK neoplasms of 1.77/100,000 per year. There is geographical variation in the frequency of the different subtypes and in Europe peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL) and angioimmunoblastic T-cell lymphoma (AITL) account for about three quarters of all cases. NK -cell lymphomas (NKTCL) are more common in Asia and are associated with Epstein-Barr virus (EBV). The human T-cell leukaemia virus (HTLV-I) is aetiologically linked to adult T-cell leukaemia/lymphoma (ATL).
The International T cell Lymphoma Project (ITLP) (Vose *et al*, 2008) studied 1314 cases of PTCL and NKTCL from 22 centres worldwide. Misclassification had occurred in 10.4% of cases. The distribution and outcome for the different subtypes is summarised in Table 3.

Presentation, diagnosis and staging

Extranodal presentation is common in PTCL and this often contributes to a delay in diagnosis (Ascani *et al*, 1997; Lopez-Guillermo *et al*, 1998; Arrowsmith *et al,* 2003). When compared to aggressive B-cell lymphomas, patients tend to present with more advanced disease, a poorer performance status and an increased incidence of B-symptoms. Para-neoplastic features are well described including eosinophilia, haemophagocytic syndrome and autoimmune phenomena (Falini *et al*, 1990; Gutierrez *et al,* 2003). The latter are particularly seen in AITL.

Diagnosis is based on examination of peripheral blood or tissue biopsy for histological features supplemented by detailed immunohistochemistry, flow cytometry, cytogenetics and molecular genetics. Expert haematopathology review is essential for the correct classification of the different subtypes. Unlike B-cell lymphomas, there is no simple test for clonality and this should be established by polymerase chain reaction (PCR) for rearrangement of T-cell receptor genes. Details of diagnosis are the subject of a separate guidelines document.

Staging is as for all lymphomas, including tests to assess the extent of disease (e.g. imaging and bone marrow biopsy) and to identify the features needed to assign a prognostic score. Investigations include full blood count and differential, tests of renal and hepatic function, lactate dehydrogenase (LDH), Beta2 microglobulin, albumin, serum calcium, uric acid, bone marrow biopsy, chest X-ray and computerised tomography (CT) scan of chest, abdomen and pelvis.
The role of positron emission tomography (PET)/CT scanning in PTCL is under investigation and has only been reported in the clinical evaluation of patients in a limited number of clinical studies so far (Elstrom *et al,* 2003). The data suggest that the majority (96% with different histologies in one series of 95, Casulo *et al* 2013) of T-cell lymphomas are FDG-avid although with variable intensity (Tsukamoto *et al,* 2007; Khong *et al,* 2008) but that in CTCL PET is not sufficiently sensitive or specific. PET detects additional sites of disease (eg bone, nasopharynx, muscle, liver, spleen, lung and skin) in up to 50% of patients but stage was altered in only 5% (Casulo *et al* 2013) and treatment recommendations were unchanged. PET may be more useful at detecting residual disease at the end of treatment or during follow-up but may lack

specificity and requires biopsy confirmation (Zinzani *et al*, 2009). PET may be helpful in guiding ASCT decisions but currently there is insufficient evidence to use results to support any management change during therapy. It cannot be recommended yet for routine use and must be prospectively validated in trials.
Lumbar puncture and magnetic resonance imaging (MRI) of the brain are required if there is any clinical suspicion of central nervous system (CNS) involvement but is not routinely recommended.
The above process should achieve a reliable diagnosis and assessment of a patient's stage, performance status and likely prognosis. This forms the basis of therapeutic decision making.

Recommendations – diagnois and staging

- **Diagnosis requires expert examination of tissue including a detailed phenotypic assessment. Clonality should be assessed by PCR for TCR gene rearrangements. This is the subject of a separate BCSH guideline.**
- **Staging should include blood and bone marrow examination and radiology as well as assessment of performance status and prognostic factors to allow assignment of a prognostic score and planning of therapy**
- **Lumbar puncture/MRI of brain is not routinely required in the absence of CNS symptoms or signs.**
- **PET scanning is not established in the routine staging of PTCL**
- **The T-cell malignancies are rare and often complex diseases. Diagnosis and management should be discussed in a network multi-disciplinary team meeting and those patients requiring treatment should generally be referred to a cancer centre or tertiary centre with specialist expertise.**

Prognosis

The International Prognostic Index (IPI) is well validated and in wide use for the assignment of B-lineage lymphoma patients to risk categories. It appears that the T-cell lymphomas can also be stratified effectively using the IPI although the greater proportion of cases are in the intermediate or high IPI groups which limits its usefulness (Ascani *et al*, 1997; Lopez-Guillermo *et al*, 1998). The ITLP demonstrated that the IPI was not helpful for enteropathy-associated T-cell lymphoma (EATL) and extra-nasal NK/TCL, since for these subtypes even a low IPI score was associated with a poor prognosis. Recently an attempt to produce a more T-cell specific IPI (PIT) has been published (Gallamini *et al*, 2004). This analysis of 385 cases identified four risk factors (age, LDH, bone marrow involvement and performance status) from which they defined four risk groups with 0, 1, 2 or >3 of these factors. Five year overall survivals for these groups were respectively: 62%, 53%, 33% and 18%. This finding is useful and accords with most published series suggesting 5-year survivals in the region of 30-35% when no distinction is made regarding risk grouping in the analysis (Gisselbrecht *et al*, 1998; Melnyk *et al*, 1997; Sonnen *et al*, 2005; Lopez-Guillermo *et al*, 1998). A scoring system that integrates clinical and biological features including age, performance status, LDH and Ki67 expression has also been shown to distinguish good, intermediate and poor risk groups (Went *et al*, 2006). In addition scores have been proposed for the specific

subtypes angioimmunoblastic (AIPI, Federico *et al,* 2013) and extra-nodal nasal-type NK/T cell (KIPI).

Other than CTCL, extranodal disease, whether as the primary presentation or subsequently, is associated with poorer prognosis. Pre-treatment serum protein levels also have prognostic significance (Watanabe *et al,* 2010). Tumour specific features under evaluation to assess prognosis include expression of cytotoxic molecules, nm23-H1 protein, Ki-67, *TP*63/53 gene abnormalities (Vasmatzis *et al*, 2012), chemokine receptors and gene profiles (Table 4). The expression of cytotoxic molecules e.g. T1A-1 and granzyme B, are associated with B symptoms, higher IPI, a lower complete response rate and an inferior outcome when compared with patients negative for these markers (Asano *et al*, 2005). Chemokine receptor expression that distinguishes subsets of T-helper cells correlates with histology and prognosis, for example CXCR3 is seen in AILT whilst CCR4 is associated with poor prognosis lymphomas including ATL (Ishida *et al*, 2004). Chromosomal losses and gains are common, especially del(6q), del(13q) and trisomy 7. (Nelson *et al,* 2008) Losses of 5q, 10q and 12q are associated with a better prognosis and uniparental disomy is demonstrated in about 35% of PTCL-NOS. Data show that gene expression profiles can discriminate between some of the subgroups and, more importantly, within the larger group of PTCL unspecified (Ballester *et al,* 2006; Piccaluga *et al* 2007a, Salaverria *et al*, 2008). For example the proliferation signature (Cuadros *et al*, 2007), over-expression of NF kB (Martinez-Delgado *et al*, 2005),cytotoxic T-cell derivation (Iqbal *et al*, 2010a) and over expression of GATA3 (Iqbal *et al,* 2012) identify different subgroups within PTCL-NOS which are associated with different prognoses. Other important recurrent mutations include; IDH2 and TET-2 mutations in AITL, translocations of IRF4 in ALCL, DNMT3A mutations in AITL and PTCL-NOS (Couronne *et al,* 2012). These aberrations affect hyper- methylation genes and may thus provide a rationale for demethylating agents in treatment. Small nucleolar RNA expression profiling also identifies potential new prognostic markers (Valleron *et al,* 2012). In the future it may be possible to identify new therapeutic targets using these subtype–specific gene signatures (Agostinelli *et al*, 2008).

Recommendations - prognosis

- **The IPI gives useful prognostic information in PTCL and should be calculated, but it clusters many cases in the higher risk groups**
- **Newer T-cell specific prognostic scores appear to be more discriminatory and may be valuable in prospective trials**

I Mature T-cell Leukaemias

The mature T-cell leukaemias are distinguished on the basis of the clinical features, peripheral blood morphology and immunophenotype and the presence or absence of positive serology for HTLV-I. Cytogenetics may be confirmatory. These leukaemias arise in adults with median age in the 5th and 6th decades. They are all slightly commoner in men than in women. The management for each of these categories is distinct.

1. T-Prolymphocytic Leukaemia (T-PLL)

1.1 Incidence and epidemiology

T-PLL accounts for approximately 2% of all small lymphocytic leukaemias in adults over the age of 30. There is no geographical clustering or known epidemiological link with viruses. There is a higher prevalence of T-PLL in patients with ataxia telangiectasia (AT) with a younger age of onset. (Dearden, 2012)

1.2 Presentation, diagnosis and staging

T-PLL is an aggressive malignancy presenting with splenomegaly, lymphadenopathy and a high white cell count which in half the patients is in excess of 100 x 10^9/l (Matutes *et al*, 1991). Other organs and skin may also be involved. Some patients may present with an indolent phase which inevitably progresses. The circulating prolymphocytes have a distinctive morphology and express mature T-cell markers (terminal deoxynucleotidyl transferase-negative, CD2 positive, CD3 weakly positive, CD5 positive and strong CD7 positive) with variable expression of the CD4 and CD8 antigens. Conventional cytogenetic analysis usually demonstrates complex abnormalities (Soulier *et al,* 2001). Inversion 14 is seen in 75% of cases (Brito-Babapulle *et al*, 1991) and more than half of the cases have abnormalities of chromosome 8. Two oncogenes, *TCL1* and *MTCP1*, are often over expressed (Virgilio *et al*, 1994; Madani *et al*, 1996). The *ATM* gene on 11q23 is also frequently involved in T-PLL and may be important in the pathogenesis (Stoppa-Lyonnet *et al,* 1998).

1.3 Prognosis

Overall prognosis is poor with a median overall survival of approximately 7 months in historic series of patients treated with conventional chemotherapy. In recent years survival of patients with T-PLL has improved following the introduction of the newer agents, pentostatin and alemtuzumab.

1.4 Treatment

T-PLL is relatively resistant to conventional chemotherapy. Pentostatin has been used at a dose of 4 mg/m^2 weekly for 4 weeks and then every 2 weeks to maximum response in a series of 55 patients with T-PLL. Responses were seen in 45% of cases with 9% complete remissions and median response duration of 6 months (Mercieca *et al,* 1994). A phase II multi-centre study examined the role of the humanised anti-CD52 antibody alemtuzumab (Campath-1H) in 39 previously treated patients with T-PLL (Dearden *et al*, 2001). The overall response rate (ORR) was 76% with 60% complete remissions (CR) and 16% partial remissions (PR). This included patients who had been resistant to other therapies such as pentostatin. This compares with response

rates to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) of 30% with no complete remissions and median progression-free survival of 3 months. Patients with serous effusions or hepatic or central nervous system involvement were more resistant to alemtuzumab therapy. Overall survival (OS) was significantly prolonged in patients achieving CR with a median of 24 months compared to 9 months for PR and 4 months for non-responders. Fifty percent of patients achieved second responses following relapse although a number of patients proceeded to either autologous or allogeneic stem cell transplant in first remission. In a retrospective analysis of 76 patients with T-PLL who were enrolled in a compassionate use programme in the United States and who had received one or more lines of chemotherapy, alemtuzumab was administered for 4-12 weeks at the standard dose of 30 mg three times a week following dose escalation in the first week (Keating *et al,* 2002). In this study the ORR was 50% with 37.5% CR and a median time to progression of 4.5 months for the group as a whole. In patients who achieved a CR the median survival was 14.8 months.
In a study in 32 patients treated with intravenous alemtuzumab as first line therapy, 91% achieved a remission (81% CR) and OS at 48 months was 37% (Dearden *et al,* 2011). However, a recent pilot study (UKCLL05) showed decreased efficacy when the subcutaneous route of administration was used (Dearden *et al*, 2011).
An alternative treatment strategy is to use initial chemotherapy followed by alemtuzumab consolidation. The German CLL study group have conducted a prospective trial with four 28 day cycles of FCM (fludarabine, cyclophosphamide, mitozantrone) followed by alemtuzumab given 1-3 months after completion of therapy (Hopfinger *et al*, 2012). Of 25 patients (16 therapy-naive) treated with induction chemotherapy the OR was 68% (24%CR) increasing to 95% OR (48%CR) following alemtuzumab consolidation therapy . The median OS was 17.1 months. Alemtuzumab in combination with pentostatin has also been reported to be effective (Ravandi *et al*, 2009). Other novel therapies may have utility in the treatment of refractory disease, including nelarabine, forodesine and AKT inhibitors (enzastaurin).

The poor outcome for most patients with T-PLL has led several groups to investigate dose escalation and autologous (auto) or allogeneic (allo) haemopoietic stem cell transplantation (HSCT). No randomised studies have been conducted with most reports comprising single cases. Although the information that can be drawn from these publications is limited by the fact that only successful outcomes are usually submitted as case reports, it is clear that HSCT can result in long-term survival, at least for some patients (Shvidel *et al,* 2000). One of the largest studies reported 28 patients treated with HSCT (15 auto-HSCT and 13 allogeneic) following alemtuzumab treatment (Krishan *et al,* 2010). Median overall survival from alemtuzumab for all patients was 48 months (52 months for autografts and 33 months for allografts). The relapse rate for the allo-HSCT patients was 33% compared to 60% for auto-HSCT. The transplant related mortality (TRM) was 31% and occurred particularly when full intensity conditioning was used. This outcome was compared to a group of 23 patients who did not undergo HSCT but achieved a CR following alemtuzumab and survived > 6 months, who had a median survival of 20 months. The 5-year survival rate was 34% for those patients who received a transplant compared to 0% for those who did not. Many of these allo-SCT recipients were included in the retrospective analysis reported by the European Group for Blood and Marrow Transplantation (EBMT) and the Royal Marsden Consortium

(Wiktor-Jedrzejczak *et al*, 2012). This study included 41 patients with a median age of 51 (24-71) years; median time from diagnosis to treatment of 12 months, and the majority transplanted for chemo-responsive disease (11 in CR, 12 in PR, 13 with stable or progressive disease). Donors were HLA-identical siblings in 21 patients and matched unrelated donors in 20 patients and reduced-intensity (RI) conditioning regimens were utilised for 31% (n=13). With a median follow-up of surviving patients of 36 months, 3-year relapse-free survival (RFS) and OS was 19% (95% CI, 6-31%) and 21% (95% CI, 7-34%), respectively. Multivariate analysis identified TBI and a short interval between diagnosis and HSCT as factors associated with favorable RFS. Three-year non relapse mortality (NRM) and relapse incidence were each 41% with the majority of relapses occurring within the first year. Other smaller reports of allo-HSCT, (Gadaret *et al,* 2001; De Lavallade *et al,* 2006; Collins *et al,* 1998; Tanimoto *et al,* 2005) have suggested the outcome is equally good following conventional and reduced intensity conditioning. Considering the significantly greater toxicity of standard intensity conditioning, reduced intensity procedures would seem preferable in this group of patients. Since chemotherapy alone is so unsuccessful in T-PLL it is likely that a graft versus tumour effect plays an important role in disease control following allo-HSCT. Strategies to maximize this effect, such as treatment of incomplete donor chimerism or minimal residual disease with donor lymphocyte infusions (DLI) should therefore be considered.

1.5 Recommendations – T-PLL

- **Intravenous alemtuzumab should be used as first line therapy for T-PLL. (GRADE 1B)**
- **Patients failing to respond should receive the combination of alemtuzumab plus pentostatin or another purine analogue (GRADE 1C)**
- **All eligible patients should proceed to either autologous or allogeneic stem cell transplant in first remission. (GRADE 1C)**
- **Patients should be entered into clinical trials wherever possible**

2. T-Large Granular Lymphocytic Leukaemia (T-LGL)

2.1 Background, incidence and epidemiology

Clonal disorders of large granular lymphocytes (LGL) are rare (less than 3% of all cases of small lymphocytic leukaemias and 2-5% of PTCL). T-LGL leukaemia is characterised by a persistent (> 6 months) increase in peripheral blood (PB) LGLs and affects adults with a median age of 55 years and equal gender distribution. It arises more commonly in patients with auto-immune disorders, particularly rheumatoid arthritis (Sokal and Loughran, 2006). This association has led to the hypothesis that T-LGL leukaemia arises on a background of sustained immune stimulation. There may also be activation of pro-survival pathways interfering with FAS signalling. The recent discovery of somatic mutations of STAT3 in around a third of both T and NK- LGL leukaemias confirms the clonal nature of these disorders and provides new insights into the molecular pathogenesis. (Koskela *et* al, 2012) STAT3 activation is associated with an anti-apoptotic phenotype.

2.2 Presentation, diagnosis and staging

T-LGL leukaemias typically have an indolent clinical behaviour with a median survival of > 10 years.

Splenomegaly is seen in about two thirds of patients but lymph node enlargement is rare. The lymphocytosis is usually between 2 and 20 x 10^9/l. Cytopenias are the most common indication for treatment. Eighty-five percent of patients develop neutropenia at some time during the disease course and in 50% this is severe (< 0.5 x 10^9/l). Anaemia and thrombocytopenia are less common, and seen in approximately 50% and 20% of patients respectively. A variety of autoimmune disorders, including haemolytic anaemia, pure red cell aplasia, thrombocytopenia and rheumatoid arthritis, may be associated. Patients with STAT 3 mutations are more likely to have symptomatic disease, neutropenia and associated rheumatoid arthritis.

Hypergammaglobulinaemia and, more rarely, hypogammaglobulinaemia are documented in a proportion of patients.

Most LGL leukaemias (80-90%) are CD3 positive with co-expression of TCR αβ, CD8, CD16 and CD57, with CD56 being negative. Uncommon variants include CD4+ cases and those with TCR $\gamma\delta$. The rare CD4+ cases have been seen in association with an underlying non-haemopoietic malignancy. In more than half of cases CD94 and KIR antigens are expressed. Cytotoxic proteins, TIA 1 and granzyme B and M are expressed. Bone marrow (BM) histology is characteristic with a mainly interstitial and intrasinusoidal infiltrate of CD8+ T-cells in association with ‘reactive’ nodules containing polyclonal B- and T-cells. It is important to establish clonality by PCR since transient and more persistent polyclonal reactive expansions of T-LGLs are common (Semenzato *et al*, 1997). Oligoclonal and sometimes clonal expansions of T-LGLs can occur in a number of situations including: following allogeneic SCT, in association with B-cell malignancies and in imatinib-treated patients with chronic myeloid leukaemia. The finding of a cloncal T-cell population should therefore be interpreted with caution, and always in the clinical context.

Rarely, T-LGL leukaemia presents with a much more aggressive clinical behaviour, usually in younger individuals (Alekshun *et al*, 2007). Characteristically, patients have B

symptoms, hepato-splenomegaly, cytopenias and LG lymphocytosis. T-LGL leukaemia may also undergo a high- grade transformation although this appears to be a very rare occurrence (Matutes *et al,* 2001a).

2.3 Prognosis

In contrast to the other mature T-cell leukaemias median survival is good (14.5 years in one series; Osuji *et al,* 2006). A retrospective review of 286 patients with T-LGL leukaemia identified anaemia, severe neutropenia and lymphopenia as poor prognostic factors (Nowakowski *et al*, 2006). Aggressive T-LGL leukaemia and high grade transformation have a much poorer prognosis.

2.4 Treatment

T-LGL leukaemia is often asymptomatic and up to half of patients may not need therapy. Treatment is usually indicated for symptomatic cytopenias and the aim of therapy is to correct these. The decision to treat is based on: significant symptomatic anaemia (<9 g/dl) and/or the need for transfusion; severe neutropenia (< 0.5 $x10^9$/l) associated with infection; severe thrombocytopenia (< 50 x 10^9/l); or any combination of these. A variety of agents have been used and reported in small case series. The best established of these for first-line single-agent therapy are low-dose methotrexate (10 mg/m^2/week) (Loughran *et al*, 1994, Osuji *et al*, 2006), cyclophosphamide (50-100 mg/day, orally), and ciclosporin (5-10 mg/kg/day, in 2 divided doses, titrated to achieve response) (Sood *et al,* 1998; Brinkman *et al,* 1998; Battiwalla *et al*, 2003), which achieve responses in 50 to 75% of patients. Prolonged treatment (3-4 months) is often necessary to achieve a response and responders usually require long term maintenance. The mechanism of action of these agents relies on immunosuppressive/ modulatory effects, probably by reducing circulating FAS ligand levels, rather than cytotoxicity. Correction of cytopenias and symptomatic improvement with therapy may be achieved without eradication of the clonal T-cells.

Patients who fail first-line therapy may benefit from purine analogues (fludarabine, cladribine, pentostatin) (Sternberg *et al*, 2003; Mercieca *et al,* 1994; Tsirigotis *et al,* 2003; Witzig *et al,* 1994). Fortune *et al* (2010) reported a 75% response rate in 9 T-LGL patients treated with pentostatin and found this to be a less toxic and more effective therapy than ciclosporin or methotrexate in their series of 25 patients. Combination therapy with fludarabine, dexamethasone and mitozantrone has been used (Tse *et al,* 2007). Steroids and growth factors may be beneficial in achieving rapid, but usually short-lived, improvement in cytopenias (Lamy *et al*, 1995). Long term steroid therapy should be avoided. Alemtuzumab has also been effective in case reports and small series (OR 50%) where patients have been refractory to all other approaches (Ru *et al,* 2003; Rosenblum *et al,* 2004; Mohan *et al* ,2008). Splenectomy can sometimes assist in relieving refractory cytopenias, especially those related to autoimmune haemolytic anaemia (AIHA) or immune thrombocytopenia (ITP) (Loughran *et al,* 1987). New therapies, tipifarnib, anti- CD2, anti-CD122 and anti IL-15, are being investigated in phase I and II studies. The JAK/STAT3 pathway may also be a therapeutic target. Patients with aggressive T-LGL leukaemia or those with high grade transformation should receive more intensive combination chemotherapy but there is insufficient evidence to support the selection of any specific regimen.

2.5 Recommendations T-LGL

- **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 (<9 g/dl) and/or the need for transfusion; severe neutropenia (< 0.5 x10^9/l) associated with infection; severe thrombocytopenia (< 50 x 10^9/l); or any combination of these.**
- **Oral ciclosporin or weekly oral low dose methotrexate (10 mg/m^2/week) are effective in more than 75% of cases (GRADE 1B)**
- **Responses may be enhanced by the use of growth factors (erythropoietin and/or GCSF) (GRADE 1B)**
- **Second line treatments include purine analogues (pentostatin), cyclophosphamide and alemtuzumab (GRADE1B)**

3. Chronic Lymphoproliferative disease of NK cells (CLPD-NK)

This is a provisional entity in the new WHO classification characterised by a persistent (> 6 months) increase in PB NK cells (usually > 2 x 10^9/l). This condition occurs in adults with a median age of 60 years and equal gender distribution. Unlike aggressive NK leukaemia there is no racial disposition or association with EBV.
It is very difficult to distinguish between neoplastic and reactive NK cells. Morphologically these cells are identical in appearance to T-LGLs but have an NK cell phenotype (CD2 positive, CD3 negative, CD4 negative, CD8 negative, CD16 positive, CD56 positive, CD57 negative) (Sokol and Loughran, 2006). The most frequently observed cytogenetic abnormality in NK-cell leukaemia is del(6q) (Man, 2002).
It is more difficult to establish clonality for NK-cell populations and a diagnosis of chronic NK- cell leukaemia therefore requires evidence of systemic disease, e.g. B symptoms, infiltration of bone marrow, spleen or liver. CLPD-NK can occur in association with other malignant and autoimmune conditions. The clinical behaviour and management is the same as for T-LGL leukaemia.

4. Aggressive NK-cell Leukaemia

4.1 Background, incidence and epidemiology

The overall frequency of NK-cell leukaemias is rare, accounting for only 10% of all LGL proliferations, but they are significantly more common in Asian countries. The geographic distribution is likely to be due to both genetic and environmental factors and is almost always associated with EBV. The disease occurs almost exclusively in younger adults (median age 39 years) and is slightly commoner in males (Oshimi, 2007).

4.2 Presentation, diagnosis and staging

Presentation is usually acute with B symptoms (particularly fever), jaundice, lymphadenopathy, hepatosplenomegaly, 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 demonstrate a CD2-, sCD3-, CD3 ε+, CD56+, CD57-, CD16 + (75%) phenotype with germline (T-cell receptor) TCR genes. High levels of FAS ligand can be found in the serum. In most cases there is clonal integration of EBV (Kawa-Ha *et al,* 1989). The commonest cytogenetic abnormalities are del (6q), del (11q) and del (17p).

Rare cases may evolve from extra-nodal NK/T cell lymphoma (which is covered in the section on extranodal PTCL), or chronic lymphoproliferative disorders of NK cells (discussed above) (Hasserjian *et al,* 2007). Although there are some common features, including the presence of EBV, aggressive NK cell leukaemia is distinct from extranodal NK/T cell lymphoma by virtue of: the younger age (almost a decade), the high frequency of hepatosplenic and PB involvement, the low frequency of skin involvement, disseminated disease and the rapidly fatal outcome despite treatment.

4.3 Prognosis

The disease course is typically fulminant with a very poor prognosis (OS 2 months). (Suzuki *et al,* 2004)

4.4 Treatment

The disease is typically chemo-resistant. Intensive acute lymphoblastic leukaemia (ALL)-like therapy regimens are used with inclusion of CNS prophylaxis (Shapiro *et al,* 2003). Consolidation with a HSCT should be considered for eligible patients achieving remission (Kimura *et al*, 2012) and patients allografted with chemo-responsive disease have a superior outcome (Ennishi *et al*, 2011).

4.5 Recommendations - Aggressive NK-cell Leukaemia

- **Rare aggressive NK- cell leukaemias occurring in younger adults require a different therapeutic approach and consideration of stem cell transplantation (GRADE 2C)**
- **Patients should be entered into clinical trials wherever possible**

5. Adult T-cell Leukaemia lymphoma (ATL)

5.1 Background, incidence and epidemiology

ATL is caused by the retrovirus, human T-cell lymphotropic virus I (HTLV-I), which is endemic in Japan, the Caribbean, Africa, South America and parts of the south-eastern USA. (Proietti, *et al,* 2005). In the UK the disease is seen predominantly in patients of Afro-Caribbean descent. HTLV-I infection affects 15-20 million individuals world-wide although 95% of these are likely to remain asymptomatic carriers, with an estimated lifetime risk of developing ATL of 1-5%. The development of ATL from HTLV-I infected CD4+ lymphocytes is likely to be due to the effects of the Tax viral transactivator protein (Matsuoka and Jeang, 2007). The tumour is derived from regulatory T cells which express Fox P3 and show integration of the HTLV-I provirus in the DNA**.** Gene expression profiling shows a homogeneous molecular signature with high expression of HTLV-1 induced genes. (Iqbal *et al,* 2010a) Aberrant expression of certain genes eg tumour suppressor in lung cancer 1 (TSLC1) have provided novel markers in acute-type ATL. (Sasaki *et al*, 2005; Pise-Masison *et al*, 2009)

5.2 Presentation, diagnosis and staging

ATL is divided into 4 different clinical subtypes: acute (leukaemic) (57%), lymphoma (19%), chronic (19%) and smouldering (5%) (Shimoyama,1991). In the ITLP 126 patients (9.6% of all PTCL) were identified with ATL of either acute (13%) or lymphoma (87%) type, 25% of whom came from Japan (Suzumiya *et al,* 2009). The median age was 62 years with a M:F ratio of 1.2:1. The peak age incidence is about a decade earlier in cases from the Caribbean. The main clinical manifestations of ATL include lymphadenopathy (in up to 80% of patients), hepatosplenomegaly (up to 67%), skin lesions (up to 60%), osteolytic lesions (up to 10%), central nervous system lesions (up to 10%), and hypercalcaemia (up to 63%) (Tannir *et al,* 1985). B symptoms and extranodal involvement are both present in about a third of patients. Gastro-intestinal tract involvement is frequent in aggressive ATL. The acute form is characterised by a rapidly increasing white cell count and hypercalcaemia. In contrast the lymphoma type has $< 4.0 \times 10^9$/l lymphocytes. The smouldering form of the disease is characterized by a normal peripheral blood leucocyte count and infiltration of skin. Patients with the chronic type also have mild clinical signs (skin, lymphadenopathy, hepatosplenomegaly, circulating ATL cells) and symptoms and both chronic and smouldering forms of the disease have an indolent course but progress to the acute form after a variable period of time. Patients are immunocompromised and opportunistic infections are common including, *Pneumocystis jiroveci* pneumonia ('PCP'), aspergillosis or candidiasis, *strongyloidiasis* and cytomegalovirus infection (White *et al*, 1995). Strongyloides serology is recommended at diagnosis to ensure appropriate treatment prior to commencing therapy (Ratner *et al,* 2007).
ATL cells have a characteristic morphology ("flower cells") and phenotype which is invariably CD4 positive and CD25 positive. In contrast to T-PLL, CD7 is commonly negative. Genetic abnormalities are frequent but there are no consistent changes. Mutations of *TP53* occur in 20-30% of patients with an increased incidence in more advanced disease. Array comparative genomic hybridization (CGH) has shown different patterns of genomic alteration for the lymphoma and acute subtypes. In the acute type gain of 3 is common whilst the lymphoma subtype is associated with gain of 7 and loss of 13.

Soluble interleukin-2 receptor is elevated in all ATL patients and HTLVI carriers, and is better than LDH as a tumour marker. Monoclonal integration of HTLV-I proviral DNA is found in all cases.
However, the presence of morphologically and immunophenotypically characteristic cells together with serological evidence of HTLV-I antibodies is the requirement for the diagnosis (Shimoyama, 1991).

5.3 Prognosis

The prognosis for acute and lymphoma subtypes is poor with a median survival of only 6.2 and 10.2 months, respectively. The median survival time for patients with the chronic form of the disease is 24.3 months. Four-year survival has been reported to be 5% for the acute type, 5.7% for the lymphoma type, 26.9% for the chronic type, and 62.8% for the smouldering type (Shimoyama, 1992). High LDH, high WBC, hypercalcaemia, age >40 years, more than 3 involved lesions and poor performance status have been associated with poor survival. Additional factors associated with a poor prognosis include thrombocytopenia, eosinophilia, bone marrow involvement, CCR4 expression and *TP53* mutation. However, in the ITLP series the IPI was the only independent predictor of survival (Suzumiya *et al,* 2009), although only 18.5% were in the good prognosis category and this study applied mainly to the lymphoma subgroup.

5.4 Treatment

Treatment decisions are based on the sub-classification and prognostic factors such as PS, LDH, number of involved sites and age. Asymptomatic patients with smouldering or favourable chronic-type ATL should be monitored.

<u>Conventional Chemotherapy</u>

Despite significant advances in understanding the pathogenesis of ATL, results of treatment remain disappointing (Bazarbachi *et al*, 2004; Taylor and Matsuoka, 2005). Traditional experience with combination chemotherapy has been of limited success, possibly due to the intrinsic resistance of ATL cells as well as to the associated immunosuppression and the frequent poor performance status of the patients. Multi-organ failure at presentation (kidney, liver) often limits the ability to deliver intensive regimens. Over-expression of the multi-drug resistance gene and mutations of the *TP53* gene have been described and probably contribute to the drug resistance.
The chronic and smouldering varieties of the disease may not require treatment for months and there is no evidence that patients benefit from early chemotherapy.
In the lymphoma and leukaemia sub-types single agent chemotherapy has produced relatively low response rates and nucleoside analogues such as pentostatin and cladribine have been of limited value. A number of trials have investigated the feasibility and efficacy of combination regimens. These regimens are generally associated with an increased response rate (although mostly still < 50%), but response duration and overall survival remain short (usually < 1 year) and there are no long-term survivors.

A report from the Japan Clinical Oncology group (JCOG) showed an improved response rate in younger patients for intensified combined treatment with VCAP (combination with vincristine, cyclophosphamide, doxorubicin and prednisolone) /AMP (doxorubicin, ranimustine and prednisolone)/VECP (vindesine, etoposide, carboplatin

and prednisolone) compared to CHOP-14 (cyclophosphamide, doxorubicin, vincristine and prednisolone) alone (40% vs 25%, p=0.02). It also showed improved 3 year survival (24% vs 13%) (Tsukasaki *et al*, 2007). Another study of CHOP-14 has demonstrated 66% overall response (25% CR) amongst 61 patients with median survival of 13 months (Yamada *et al,* 2001). Other reported chemotherapy combinations have also yielded some success in a more elderly, less well, patient cohort, including RCM (vindesine, doxorubicin, pirarubicin, cyclophosphamide, etoposide, ranimustine, methotrexate, peplomycin, prednisolone) (Uozumi *et al,* 1998), OPEC/MPEC (vincristine, etoposide, prednisolone and cyclophosphamide /methotrexate, etoposide, prednisolone and cyclophosphamide) (Matsushita *et al,* 1999) and ATL-G-CSF (vincristine, vindesine, doxorubicin, mitoxantrone, cyclophosphamide, etoposide, ranimustine and prednisolone with G-CSF support (Taguchi *et al,* 1996). However, none of these combinations have equalled survival benefits reported by the JCOG. These regimens share a basis of more frequent cycles of chemotherapy (given weekly) an approach which may offer greater advantages in achieving and maintaining disease control in ATL. G-CSF support is usually needed to facilitate chemotherapy. Matsushita *et al* (1999) suggest an oral regimen utilising etoposide 25 mg daily with prednisolone 10 mg and report superior results to some multi-drug regimens. The benefits of combination chemotherapy are largely confined to the lymphoma sub-group. In one Phase II Japanese trial of intensive multi-agent therapy less than 20% of leukaemia patients achieved a CR and survival was only a few months (Yamada *et al*, 2001).
Although response rates to induction treatment may be relatively high (60-70%), relapse is inevitable. Consolidation and maintenance strategies therefore need to be considered and suitable patients should be referred for allogeneic HSCT.
Specific antimicrobial prophylaxis, in particular for strongyloides if the patient is seropositive, should be considered as serious opportunistic infections are common and have a significant impact on treatment-related morbidity/mortality.

Anti-retroviral Therapy

A number of phase II studies of the combination of the anti-retroviral drug zidovudine (ZDV) and interferon-α (IFN-α) have reported significant activity in patients with ATL, including in those who had failed prior cytotoxic chemotherapy (Gill *et al*, 1995; Hermine *et al* 1995; Bazarbachi and Hermine, 1996; White *et al*, 2001; Hermine *et al*, 2002; Matutes *et al*, 2001b). Response rates up to 92% with median OS of 11 months (28 months for CR) were recorded in previously untreated patients (Hermine *et al*, 2002). For the leukaemia sub-group of patients, in particular, these results are superior to any chemotherapy regimens (Bazarbachi *et al*, 2011). A recent meta-analysis on 254 patients confirmed that response rate and survival are improved when these drugs are used as first line therapy (Bazarbachi *et al*, 2010). Five year OS was 46% for patients who received antiviral therapy alone compared to 14% for those receiving chemotherapy alone and 12% for those receiving both. Patients with chronic and smouldering subtypes had 100% survival after 10 years. For those patients with acute leukaemic subtype the 5- year survival rate was 82% for those achieving a CR with antiviral therapy. A retrospective study of 73 patients in the UK with acute (leukaemia) or lymphoma types of ATL demonstrated benefit for the addition of anti-viral therapy at any time during treatment, with improved survival and reduced risk of death. (Hodson *et al*, 2011) Lymphoma patients had less benefit and chemotherapy was unsuccessful in

anti-viral therapy failures. The anti-viral combination has a good safety profile and can be administered at high doses as well as being combined with chemotherapy (Besson *et al*, 2002) and other anti-viral drugs such as lamuvidine. The exact dose and duration of therapy is undetermined. In the UK series Interferon was administered at a dose of 3 million units daily with ZDV given at 250mg bd and continued for up to 5 years if tolerated. Patients who harbour *TP*53 mutations are less likely to respond to antviral therapy. In the future it may be possible to better predict response to anti-viral therapy (Datta *et al*, 2006; Ramos *et al*, 2007) and also to test synergy with other novel agents such as monoclonal antibodies.

Monoclonal Antibodies

Conjugated and unconjugated monoclonal antibodies (anti-CD25, anti-CD4, anti-CD52, anti-CCR4, anti-transferrin receptor), have all been tested in small numbers of patients. (Waldmann, 2007; Mone *et al,* 2005; Ravandi and Faderl 2006; Sharma *et al,* 2008; Ishida *et al,* 2006; Moura *et al,* 2004). A Phase II study of a defucosylated humanised anti-CCR4 monoclonal antibody, mogamulizumab, yielded an ORR of 50% and median PFS of 5.2 months in relapsed pateints with ATL (Tobinai *et al* 2012). Further clinical trials are needed to better define the roles of these agents.

Novel Agents

Several possible new approaches to the treatment of patients with ATL are being investigated. In a Phase II trial the combination of arsenic trioxide and interferon (IFN)-α reduced Tax expression, reversed the Tax-induced constitutive NF-κB activation and demonstrated activity in some patients. However, most responses were short-lived (Hermine *et al*, 2004).

The proteasome inhibitor, bortezomib, affects multiple survival pathways in HTLV-I-positive T-cells and may have a potential therapeutic role (Nasr *et al*, 2005). As yet no clinical trials have been reported. All-*trans*-retinoic acid (ATRA) has been shown to induce partial responses, especially in skin disease, and may be useful in combination. Immune-based therapy with Tax-directed vaccines may also have a role in the future.

Auto- and allo-HSCT

There appears to be minimal long-term benefit in autografting patients with ATL with the majority of patients relapsing or dying of transplant complications within 1 year of transplant (Tsukasaki, *et al*, 1999, Watanabe *et al*, 2001). Although efficacy may be improved if interferon-α therapy is offered post-HSCT, the follow-up of reported cases has been short (Fujiwara *et al*, 2002).

Prolonged disease free survival has been described after allo-HSCT. Many of the reports are derived from retrospective analyses of the Japanese Registry Data (Utsunomiya *et al*, 2001; Kami *et al*, 2003; Fukushima *et al*, 2005, Okamura *et al*, 2005) with the largest analyses reported recently (Ishida *et al*, 2012; Hishizawa *et al*, 2010). These studies included 586 and 386 recipients of allo-SCT respectively, including related donors, unrelated donors and unrelated cord blood donors.The 3-year overall survival for the entire cohort was 36% (32%-41%) and 33% (95% confidence interval [CI], 28%-38%) respectively. Age and performance score have been identified as

significant predictors of survival and since the median age at presentation with ATL is approximately 60 years, RI-conditioning regimens are favoured for the majority of patients (Ishida *et al*, 2012, Hishizawa *et al*, 2010).

Among patients who received related transplants, donor HTLV-I seropositivity adversely affected disease-associated mortality (Hishizawa *et al*, 2010) and thus selection of HTLV1-seronegative donors has been recommended. The use of unrelated cord blood has been associated with lower survival (3 year OS of 17%) most likely a result of higher TRM (Hishizawa *et al*, 2010). Another report from the Japanese demonstrated that the development of mild-to-moderate (Grade 1-2) acute graft-versus-host disease (GVHD) conferred a lower risk of disease progression and a beneficial influence on survival of allografted patients with ATL (Kanda et al, 2012). In contrast, although the development of grade 3-4 acute GVHD was associated with lower disease-associated mortality compared with the absence of acute GVHD, it was associated with a higher risk for TRM (HR, 3.50; $P < .001$) and thus no survival benefit was observed. (Kanda et al, 2012).

Remission status at transplant has been consistently shown to be an important prognostic factor for outcome (Ishida *et al*, 2012, Hishizawa *et al*, 2010), which suggests that strategies optimising chemo-immunotherapeutic and/or anti-viral approaches prior to allo-SCT are required.

Failure to detect HTLV-1 genome after allo-HSCT has been associated with prolonged remission and disease free survival after allografting (Okamura *et al,* 2005, Nakase *et al*, 2008). ATL relapses have been successfully managed with a reduction in immune suppression or DLI (Harashima *et al*, 2004; Okamura *et al*, 2005) and clinical responses have been associated with HTLV-1-specific immunological responses (Harashima *et al,* 2004). The International Consensus meeting proposed that early allogeneic SCT should be considered for all suitable high risk patients (Tsukasaki *et al,* 2009)

Prevention

The low acquisition rate of disease in seropositive individuals together with the lack of predictive factors and cost constraints mean that surveillance/screening strategies are unlikely to be introduced. Lowering transmission by screening of blood donors and abstention from breast feeding by HTLV-I positive mothers can result in a substantial decrease in carrier rates. Vaccination is not available.

5.5 Recommendations - Adult T-cell Leukaemia lymphoma (ATL)

- **Exclude co-infection with strongyloides prior to commencing therapy.**
- **Appropriate antimicrobial prophylaxis during therapy should be instituted for seropositive patients.**

- **Smouldering & Chronic**
  - **no benefit from early chemotherapy therefore watch and wait**
  - **Zidovidine (ZDV) + Interferon-α +/- monoclonal antibodies may be considered (especially in chronic ATL) in the context of a clinical trial (GRADE 1B)**

- **Lymphoma type**
  - **Induction with CHOP or alternative multi-agent regimen plus G-CSF (GRADE 1B) with Concurrent ZDV + Interferon-α (GRADE 1B)**
  - **ZDV + Interferon-α maintenance +/- Monoclonal antibodies (MoAbs) OR Allogeneic transplant in 1st CR for eligible patients (GRADE 2C)**

- **Leukaemia (Acute) type**
  - **Induction with anti-retoviral therapy alone (ZDV + Interferon-α**
  - **OR Induction with CHOP or alternative multi-agent regimen plus G-CSF(GRADE 1B) + Concurrent ZDV + Interferon-α**
  - **Allo HSCT in 1st CR for eligible patients (GRADE 1B)**
  - **OR ZDV + Interferon-α maintenance +/- MoAbs (GRADE 2C)**
  - **OR consolidation with novel agents e.g. Arsenic trioxide, αIFN; proteasome inhibitor in clinical trials**

- **CNS prophylaxis should be considered using the same criteria as for diffuse large B-cell NHL (GRADE 2C)**
- **II. Nodal PTCL**

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

6.1 background, incidence and epidemiology

PTCL-NOS is the largest group of T-cell lymphomas, accounting for around half of the cases seen and 3.7% of all lymphomas. It is almost certainly not a single biological entity but at the present time it is a useful term to encompass the large proportion of T-cell malignancies that do not fall into the more distinct diagnostic groups described in this guideline and recognised in the WHO classification (Harris *et al,* 1997; Swerdlow *et al*, 2008). They are aggressive lymphomas, mainly of nodal type, but extranodal involvement is common. Attempts to subdivide this group have been made but there is little evidence that this is clinically relevant given our current level of understanding and the diagnostic reproducibility of such strategies has been poor. It is likely that better understanding of these diseases will lead to useful subdivisions in the future..Of note, up to 20% of cases diagnosed as PTCL-NOS have a gene expression profile characteristic of AILT, whilst another subgroup have a cytotoxic T-cell profile (Iqbal *et al*, 2010a).

6.2 Presentation, diagnosis and staging

This is as outlined in the introductory section. Most cases have a $CD4^+$/CD8 phenotype and array CGH studies show loss of 9p, 5q or 12q in about 30% of patients.

6.3 Prognosis

Prognostic information and assessment, as summarised in the introductory section, is largely based on data from PTCL-NOS since this is the commonest category once ALK^+ ALCL has been removed. The 5-year failure-free survival (FFS) and OS is about 20% and 30% respectively.The ITLP study identified that a high number of transformed cells in tissue biopsies was a significant prognostic factor and suggested that this,

together with the IPI, could be used to risk-stratify the sub-group of patients with PTCL-NOS. (Weisenburger *et al,* 2011)

6.4 Treatment

The conventional chemotherapy regimens used to treat aggressive NHL (e.g. CHOP) have produced disappointing results in PTCL-NOS when compared to its B-cell counterpart or ALK-pos ALCL. This poor outcome for PTCL seems to be a combination of problems at all stages of the disease with lower initial response rates and a higher proportion of resistance and early death as well as a greater tendency to relapse after CR, mainly within the first 1-2 years. Unfortunately CHOP remains the most commonly used first line treatment despite the fact that it has never been established as the preferred or most effective treatment for non-ALK-pos PTCLs. Currently, however, there are insufficient data to recommend an alternative and trials are badly needed to explore new regimens.

<u>First line therapy</u>

CHOP has been evaluated in first-line treatment of PTCL-NOS in a number of studies. Allowing for the caveats in interpretation mentioned above, it achieves a CR rate of around 50% and 5-year overall survival of 30% (Gisselbrecht *et al*, 1998; Melnyk *et al*, 1997; Sonnen *et al*, 2005; Lopez-Guillermo *et al*, 1998). Higher relapse risks than for B-cell lymphomas are noted in these studies, contributing to a high rate of treatment failure in the first 1-2 years (Coiffier *et al*, 1990; Gallamini *et al*, 2004). These results have led to investigation of intensification of therapy.

There are examples of phase II and III studies addressing intensification, either with alternative chemotherapy, autografting or both. There is a tendency for single arm prospective data to show promising results with intensive approaches (e.g. CEOP-B (epirubicin instead of doxorubicin) + bleomycin, 5-year OS 49%) (Sung *et al,* 2006) but this has not been confirmed in a randomised setting (Simon *et al,* 2010). A large retrospective comparison of CHOP and more intensive therapy from the M.D. Anderson Cancer Centre found no difference in outcome between the two (Escalon *et al*, 2005), with 3-year OS 62% vs 56% respectively, and 43% vs 49% after exclusion of ALCL. The GOELAMS group conducted a small prospective randomised front –line study in 88 patients comparing a VIP (etoposide, ifosfamide, cisplatin) reinforced ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) regimen with CHOP-21. No significant difference was observed between the two arms in 2 year EFS. (45%). (Simon *et al,* 2010). The Nordic group demonstrated some improvement for MACOP-B randomised against CHOP (Jerkeman *et al*, 1999). Etoposide added to CHOP has shown mixed results (Karakas *et al*, 1996). Seven high-grade NHL studies by the German study group showed that young good risk patients had improved 3-year EFS (71% vs 50%) if etoposide was added to CHOP (14 or 21) (Schmitz *et al*, 2010). But many patients in the series had ALCL, and if the ALK-pos ALCL are excluded the difference is no longer significant. The GELA group studies in all high-grade lymphomas found ACVBP to be superior to CHOP in patients aged 60-70 years but failed to show any difference in younger patients for this or other alternative regimens (Tilley *et al*, 2003; Delmer *et al*, 2003). Furthermore, the addition of bortezemib to ACVBP was not superior to ACVBP alone and was associated with increased toxicity. The Japanese study group have conducted a Phase II trial of CyclOBEAP (doxorubicin, cyclophosphamide, etoposide, vincristine, bleomycin, prednisolone) in 85 newly

diagnosed PTCL patients. Their results were impressive with 5 year OS of 72% and PFS 61%, and 93% 5y OS in the ALCL cases. (Niitsu *et al,* 2011). This is the only study to really suggest an advantage for adding to CHOP, and although a reasonably large cohort of patients it was not randomised.

Of particular interest is the observation from the ITLP (Vose *et al*, 2008) that the inclusion of an anthracycline in a chemotherapy regimen made no difference to outcome. This may be due, in part, to the high P glycoprotein (PGP) expression in many of the PTCLs that is associated with resistance to anthracyclines.

Most published data using alternative or intensified chemotherapy has also consolidated the patients with an autograft, which makes interpretation of the effects of chemotherapy schedules alone difficult (Mercadal *et al*, 2008). CHOP therefore remains essentially unchallenged outside clinical trials, if autografting is not considered an option for the patient at first line.

In order to improve on the results with CHOP a number of recent studies have focussed on the addition of new agents to CHOP or other novel combination treatments (Table 5) The Italian group have treated 18 evaluable patients who were given CHOP at a 4-weekly interval, together with alemtuzumab. Twelve of these patients were alive at 1 year, 11 in CR (Gallamini *et al*, 2007). An Asian study, also of CHOP and alemtuzumab, at 21 day intervals, was stopped early because of toxicity (Kim et al, 2007). The HOVON group have examined standard CHOP-14 with alemtuzumab and found a 90% ORR and median OS of 27 months (Kluin-Nelemans *et al,* 2008). There has also been an NCI study of DaEPOCH + alemtuzumab showing a PFS of 45% and OS of 48% at 3 years, with a plateau emerging on the curves (Janik *et al,* 2005). The German study group have examined the combination of alemtuzumab with FCD chemotherapy (fludarabine, cyclophosphamide and doxorubicin) which gave a 58% CR rate in the small number of patients studied, but with significant additional toxicity (Weidmann *et al*, 2010). These trials suggest that there may be an advantage in adding alemtuzumab to standard chemotherapy, albeit with increased toxicity, but this should be tested in prospective randomised trials and currently is not a strategy advised outside the trial setting. A current European study (ACT I / II) randomises patients to 14-day CHOP with or without alemtuzumab. Patients under 60 years of age are autografted in first remission. This trial has accrued well and will be the largest randomised study ever conducted in PTCL. A question remains regarding the CD52 expression in PTCL with some published data reporting around half of cases as CD52 negative (Rodig *et al*, 2006; Piccaluga *et al*, 2007b; Chang *et al*, 2007), whilst others suggest that the majority of PTCL-NOS are in fact positive (Jiang *et al,* 2009; Reimer *et al* , 2009). The discrepancy may be due to methodology since CD52 staining in paraffin embedded tissue is unreliable. In the future CD52 staining on fresh tissue should be part of any prospective trial which includes alemtuzumab therapy.

CHOP has also been evaluated in small Phase II trials in combination with botezomib (ORR 76%) (Kim *et al* , 2012) and in combination with denileukin difitox (ORR 65%) (Foss *et al,* 2013). These regimens were both well tolerated and there was a suggestion that PFS and OS may have been improved compared with CHOP alone. However these remain to be tested in randomised comparisons. The ECOG group have examined CHOP with or without bevazucimab, however the combination was associated with cardiac events resulting in early closure of the trial. .

Overall, it appears that addition to CHOP often delivers increased toxicity which outweighs the potential benefit. The benefits are unlikely to be equivalent in all

subtypes but it is very difficult to establish this in small heterogeneous trials. It will not be feasible to conduct randomised studies against CHOP for all the new agents and a more rational way of developing treatment will be required in the future.

Gemcitabine combinations are also being explored in the first-line setting e.g. CHOP, etoposide and gemcitabine (Kim JG e*t al,* 2006), dexamethasone, ifosfamide, methotrexate and gemcitabine (Dong *et al,* 2013) and the SWOG group have conducted a Phase II trial of gemcitabine, cisplatin, etoposide and methylprednisolone (PEGS). In the latter study in 33 patients (79% newly diagnosed) 39% achieved a response, but at 2 years PFS was only 12% and OS 30%. (Mahadevan *et al,* 2013). In the other studies the results have been more encouraging, with RR of up to 88% and PFS and OS rates at 2 years of 46% and 64% respectively (Dong *et al,* 2013) . In the UK, a front –line prospective randomized trial (CHEMO-T) has been initiated comparing standard CHOP-21 to the combination regimen GEMP (gemcitabine, methyl prednisolone, cisplatin) followed by the choice of autologous HSCT in first remission for suitable patients. Where possible patients should be entered into this study since clinical, biological and PET data will be collected prospectively in a large carefully controlled trial.

A number of more novel agents have been investigated in PTCL but most data, as expected, is in relapsed/refractory disease and will be summarised below. (Foss *et al*, 2011). Some of these agents may be attractive as maintenance strategies for those patients not suitable for consolidation with a HSCT.

Consolidation in 1st CR with auto-HSCT

Several groups have examined the role of dose-escalated chemotherapy with auto-HSCT support as consolidation therapy for PTCL (Mounier *et al,* 2004; Corradini *et al*, 2006; Rodriguez *et al*, 2007a; Feyler et al, 2007) (Table 6). Mounier et al reported a series of carefully case matched patients drawn from the GELA LNH 87 and 93 trials comparing HDT with combination chemotherapy (ACBVP) alone. He noted that there was no difference in DFS or OS in the 29 patients with non-anaplastic PTCL (Mounier *et al*, 2004). Long term follow-up of an Italian study of high dose sequential chemotherapy in PTCL reported a 12-year OS of only 21% in the non-ALK$^+$ cohort compared to 62% in the ALK$^+$ patients (Corradini *et al*, 2006). The intention-to-treat analysis in this prospective study showed that only 74% of patients underwent auto-HSCT because of a high incidence of disease progression during first-line treatment. In a multivariate analysis achievement of complete remission at the time of transplant predicted for superior outcome which has been corroborated in other studies (Corradini *et al*, 2006; Feyler *et al,* 2007).

A study of 74 patients with PTCL transplanted in first remission mainly using high dose chemotherapy conditioning reported a 5-year OS and PFS of 68% and 63% respectively (Rodriguez *et al*, 2007a). All patients entered into the study were however in remission at the time of transplant and the study included 23 cases of ALCL whose ALK status was not reported, which may both have significantly biased the outcome. On multivariate analysis the prognostic index for T-cell lymphoma (Gallamini *et al,* 2004) identified a poor risk subgroup with an OS of 21% at 5 years. A second study from the same group analysed outcome in poor risk cases, defined by exclusion of ALK$^+$ disease and advanced stage (Rodriguez *et al*, 2007b). These patients received

intensive induction with MegaCHOP prior to high dose therapy with BEAM (carmustine, etoposide, cytarabine, melphalan) conditioning in responders and salvage with ifosfamide and etoposide followed by BEAM in CHOP non-responders. Of 26 patients entered into this study 19 responded either to induction or salvage treatment and, after high dose therapy, 17 achieved CR. Thus, on an intention to treat basis, intensive induction followed by high dose therapy with autologous stem cell support resulted in a CR rate of 65% in poor prognosis PTCL. The 3 year OS and PFS was estimated at 73% and 53% respectively. Reimer *et al* (2009) recently published results of a prospective multicentre centre trial of upfront HSCT in PTCL (PTCL-NOS n=32; ALK^- ALCL n=13; AITL n=27). Of 83 patients enrolled onto the study, only 55 patients (66%) proceeded to HSCT. Progressive disease was the predominant reason for not undergoing HSCT, as previously reported (Mercadal *et al*, 2008). The estimated 3-year OS and PFS were 48% and 36% respectively (Reimer *et al*, 2009). The estimated 3-year OS was 71% for patients who underwent auto-HSCT compared to 11% for patients who did not.
A large prospective phase II study assessing the efficacy of up front auto-SCT for patients in CR or PR after treatment with CHOP/CHOEP has been reported recently by the Nordic group (d'Amore *et al,* 2012). Patients with ALK+ ALCL were excluded. The majority had advanced-stage disease, B symptoms, and elevated serum LDH and 115/160 of enrolled patients proceeded to auto-SCT with 83 patients alive at median follow-up of 5 years. Consolidated 5-year OS and PFS were 51% (95% CI, 43% to 59%) and 44% (95% CI, 36% to 52%), respectively.These data are consistent with results from other recent studies (Nademanee et al, 2011) confirming a role for auto-SCT in consolidation up-front.

Treatment of relapsed or refractory disease

Patients responding to further therapy and of acceptable fitness are usually considered for HSCT and whether patients should undergo allo-HSCT or auto-HSCT is contentious. Ideally this should be in the context of a trial, particularly if the stem cell source is allogeneic as this is experimental but, given the prognosis of relapsed PTCL, most clinicians would consider such approaches for any suitable patient as some evidence of efficacy does exist.

Salvage chemotherapy for relapsed or refractory disease

Re-induction or treatment of refractory disease is usually with combination chemotherapy to which about half the patients may respond. There are also a number of experimental agents that have shown promise and patients should be considered for inclusion in suitable clinical trials where available. There are no data on which to base the choice of re-induction and the conventional approach is to use a platinum-based schedule (eg DHAP or ICE), particularly when intending to consolidate with a transplant.

Novel Agents

There are emerging data of interest for other agents (Table 5). The place of these newer agents in therapy is not yet fully established although, given the poor response in PTCL-NOS to conventional chemotherapeutic agents, they are likely to be critical for

progress in the future. So far most of the data is for monotherapy but trials are underway evaluating these novel agents in combination regimens.

Bendamustine

Bendamustine has been widely adopted for therapy in B- cell malignancies, particularly indolent sub-types such as follicular lymphoma. Results have been published this year of a trial of bendamustine (120mg/m^2 days 1+2, every 21 days for 6 cycles) in 60 patients with relapsed or refractory PTCL or CTCL. (Damaj *et* al 2013) Most patients had disseminated disease, the predominant subtype was AILT, the median number of prior therapies was 1 and 45% were refractrory to the last treatment. A third of patients progressed on treatment, but ORR was 50% including 28% CR. However, PFS and OS were very short at 3.5 and 6.2 months respectively. Toxicity was acceptable. As yet there is no data of bendamustine in combination with other agents.

Purine analogues

Gemcitabine as a single agent in cutaneous and non-cutaneous T-cell lymphoma seems highly active in phase II studies (Marchi *et al*, 2005; Sallah *et al*, 2001; Zinzani *et al*, 2010). Studies of gemcitabine in combination with steroids and cisplatin (GEM-P) have yielded encouraging results in refractory patients (Arkenau *et al*, 2007; Emmanouilides *et al*, 2004; Spencer *et al,* 2007). In one study gemcitabine, oxaliplatin and dexamethasone was used as a salvage treatment for elderly patients regarded as unsuitable for high dose therapy and autograft.(Yao *et al,* 2012) The ORR was 38% with a median EFS and OS of 10 months and 14 months respectively.The treatment regimen was well tolerated in this patient population. Some of these combination regimens have been moved into the front-line setting as outlined above, including as one arm of the randomised CHEMO-T trial in the UK. Pentostatin has also been used in PTCL, but seems to be most effective in leukaemic and cutaneous sub-types (Merceica *et al,* 1994; Tsimberidou *et al,* 2004). There is only very limited data for other nucleoside analogues, including cladribine, fludarabine, clofarabine, nelarabine and forodesine.

Monoclonal Antibodies and Immunoconjugates

Alemtuzumab has been shown to have activity as a single agent in relapsed refractory patients (Dearden, 2006; Lundin *et al*, 1998). as well as in combinations eg with CHOP, some of which have been tested in the front-line setting as outlined above. A 36% overall response rate was seen with single agent alemtuzumab in a heavily pre-treated cohort of patients with PTCL (Enblad *et al*, 2004).

Of most interest is the anti-CD30 immunoconjugate , brentuximab vedotin, which has induced remarkable responses in relapsed ALCL as detailed in that section. However, other histological subtypes, including PTCL-NOS can express CD30 and trials are ongoing to evaluate efficacy of this agent in other PTCLs.

Other antibodies include those directed against CD25 and CD4 (zanolimumab) (d'Amore *et al,* 2010), and the IL2–toxin conjugate dinileukin-difitox (Dang *et al,* 2007; Foss *et al,* 2007; Waldmann *et al,* 2007),.Denileukin difitox induced responses in 48% of heavily pre-treated patients and was subsequently tested in combination with CHOP as first-line therapy. Histone Deacetylase Inhibitors

Histone deacetylase (HDAC) inhibitors have pleiotropic effects on cell cycle and apoptosis, mediated through expression of tumour suppressor genes that had

previously been silenced by acetylation. There are data on a number of HDACs including romidepsisn (depsipeptide), (Piekarz *et al*, 2004 and 2011, Coiffier *et al,* 2012), vorinostat, panobinostat and belinostat. Vorinostat is approved in the USA for treatment of CTCL and romidepsin for CTCL and PTCL. A pivotal phase II study of romidepsin was conducted in 130 patients with relapsed/refractory PTCL. (Coiffier *et al,* 2012) The ORR was 25%, including 15% CR/Cru,with median duration of 17 months. Durable responses were seen across all major histological subtypes regardless of prior therapies.Potential synergies exsist with a number of other agents, including cconventional chemotherapy and bortezomib. A randomised study comparing CHOP with or without romidepsin as first-line therapy in PTCL is underway.

Anti-Folates

A novel anti-folate, praletrexate (O'Connor, 2007, 2009,2011), has recently been approved in the US for treatment of relapsed PTCL but was declined a license in the EU. The pivotal data from the PROPEL study has now been published (*O'Connor et al,* 2011). 111 patients with relapsed/refractory PTCL were treated achieving an ORR of 29% (11% CR), a median duration of response of 10.1 months and a median OS of 14.5 months.Responses were independent of age, histologic subtype and prior therapy, including autograft. Most common toxicities were mucositis and thrombocytopenia. *In vitro* praletrexate has been shown to have synergy with gemcitabine and bortezomib and clinical trials evaluating combination therapy are ongoing.

Other agents

Alisertib (aurora kinase inhibitor) (Friedberg *et al,* 2011; Qi *et al,* 2012), lenalidomide (Zinzani *et al,* 2011), enzastaurin (protein kinase C inhibitor) and bortezomib (Zinzani *et al,* 2007) have all been reported to have activity in PTCL and are being developed in a variety of clinical studies including in combination with other agents.

Auto-HSCT for relapsed/refractory PTCL

A number of groups have reported their experience with high dose therapy and auto-HSCT as salvage for relapsed PTCL (Blystad *et al,* 2001; Song *et al*, 2003; Smith *et al*, 2007; Kewalramani *et al*, 2006). In the main these are retrospective uncontrolled studies and many include cases of ALK^+ ALCL which, as previously noted, have a better prognosis than other histological categories. Overall the efficacy of this approach, in patients with disease that was not ALK^+, was disappointing, with 5-year OS of <35% in most studies (Song *et al*, 2003; Jantunen *et al,* 2004; Zamkoff *et al*, 2004; Smith *et al*, 2007; Kewalramani *et al,* 2006,). The paper from Zamkoff specifically reported 15 ALK-negative ALCL cases that were followed up after being autografted for relapse. Thirteen of these relapsed once more and the median survival was only 72 weeks.

Allo-HSCT for relapsed/refractory PTCL

Previously most retrospective studies of allo-HSCT in T-cell lymphomas have analysed combined results for patients with nodal and cutaneous disease. The TRM for standard intensity conditioning regimens in patients with PTCL has been very high (30-50%), presumably because of more advanced age and the effects of prior therapy (Dhedin *et al*, 1999; Le Gouill *et al*, 2008). This unacceptably high toxicity and high median age of patients stimulated the development of RI- conditioning regimens.,An early pilot study

of 17 patients which included 9 PTCL-U, 4 AITL and 4 ALK- ALCL reported a NRM at 2 years of only 6% following a conditioning regimen that incorporated thiotepa, fludarabine and cyclophosphamide (Corradini *et al*, 2004). This group has recently reported the long term outcome of 52 patients with relapsed PTCL who had undergone RI-allo-SCT using this conditioning regimen (Dodero *et al*, 2012). The majority had chemosensitive disease (75%), undergone a prior auto-SCT (52%) with HLA-identical sibling donors (64%). Five-year OS, PFS and current PFS were 50% (95% CI, 36 - 63%), 40% (95% CI, 27 - 53%) and 44% (95% CI, 30-57%) respectively. DLI was effective for 8/12 (66%) patients treated for disease progression. The CI of NRM was 12% at 5 years and extensive GVHD increased the risk of NRM (33% versus 8%, P=0.04). Adverse prognostic factors were refractory disease and age over 45 years on multivariable analysis.However, this study confirms this is an effective strategy, especially for younger patients with chemosensitive disease. This is supported by similarly encouraguing results from smaller studies using different RI-conditioning regimens (Shustov et al, 2010; Jacobsen et al, 2011; Zain et al, 2011; Delioukina et al, 2012; Goldberg et al, 2012;). Further prospective trials addressing the role of RIC-allo-HSCT in T-cell lymphomas are warranted.

CNS Prophylaxis

This remains contentious in all the aggressive lymphomas. There is no consensus as to the optimal strategy or indeed which lymphomas should receive prophylaxis. The data on PTCL does not allow specific recommendations distinct from B-NHL. Guidelines on prophylaxis are being drawn up by the BCSH and have been the subject of recent reviews (Hill *et al*, 2006; McMillan *et al,* 2005). There is a 5% incidence of CNS relapse in most large studies of aggressive NHL and the factors of importance include: IPI score, LDH, involvement of extranodal sites and specific sites such as bone marrow, testis and sinuses. It seems logical to apply the same approach to prophylaxis in PTCL as for the more common diffuse large B-cell lymphoma. The nature of PTCL is that it will tendto have more cases with the high-risk features listed above and so a larger proportion of patients may receive CNS prophylaxis for that reason. T-cell phenotype alone is not an indication to use prophylaxis.

6.5 Recommendations - Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)

- **Primary treatment of PTCL-NOS should be within the context of a clinical trial if possible as standard therapy gives disappointing results (GRADE 1B)**
- **Outside trial, CHOP remains the standard therapy. Consideration should be given to consolidation with auto-HSCT (GRADE 2B)**
- **Relapsed or refractory disease should be treated with relapse-schedule combination chemotherapy and considered for Allo-HSCT with reduced intensity conditioning (GRADE 2B) or autologous stem cell transplantation (GRADE 2B) or novel therapies within a trial setting**

- **Outside a trial a number of agents show promise, particularly gemcitabine, bendamustine, praletrexate and romidepsin but the data are insufficient to recommend routine use.**
- **CNS prophylaxis should be considered using the same criteria as for diffuse large B-cell NHL (GRADE 2C)**

7. Angio-immunoblastic T cell lymphoma (AITL)

7.1 Background, incidence and epidemiology

Angioimmunoblastic lymphoma (AITL) constitutes between 13% and 24% of peripheral T-cell lymphomas (Gisselbrecht *et al*, 1998; Lopez-Guillermo *et al*, 1998; Pellatt *et al*, 2002, Reudiger et al, 2006). In the ITLP the rate was 18.5%. The annual incidence of AITL in the UK is in the order of 1 per 10^6 (GJ Dovey, EGU, Leeds, and S Dojcinov, UHW, Cardiff, written personal communications). AITL is difficult to diagnose and treat because of the presence of both B- and T-cell clones. It has a variable clinical course with autoimmune features.

7.2 Presentation, diagnosis and staging

AITL is a disease of the elderly, with most patients presenting within the sixth and seventh decades (median age 59–64 years) (Tobinai *et al*, 1988; Ohsaka *et al*, 1992; Siegert *et al*, 1995; Pautier *et al*, 1999; Attygalle *et al,* 2002, Mourad *et al,* 2008). There is no sex predilection of the disease (male to female ratio: 1·3–0·7). The patients have a wide geographical distribution and have been reported in the Americas, Europe, Asia and Africa. One small series suggests that the incidence of AITL may be higher in Hong Kong than Europe (Ruediger *et al,* 2002).

AITL typically presents with systemic illness, characterized by B symptoms (68-85%) and generalized lymphadenopathy (76 -97%), often mimicking an infectious process. In a recent prospective series, 89% of the patients had stage 3 or 4 disease as well as worse prognostic indices compared with other PTCL (Ruediger *et al,* 2006). The majority of patients have hepatosplenomegaly (52 -78%) and pruritus, and a skin rash is also seen in a quarter of patients. Polyarthritis (18%) and ascites/effusions (23-37%) (Tobinai *et al*, 1988; Siegert *et al*, 1995; Pautier *et al*, 1999), are also relatively frequent.

Laboratory investigations often show the presence of anaemia (40-57%), eosinophilia (39%), and occasionally pancytopenia. Typically, there is polyclonal hypergammaglobulinaemia (30-50%), and both the LDH (70-74%) and the erythrocyte sedimentation rate (ESR, 45%) are often elevated. A significant proportion of patients have circulating autoantibodies (66-77%), including a positive direct antiglobulin test (DAT), cold agglutinins, cryoglobulins and circulating immune complexes. Bone marrow involvement is observed in 61% and clonal T cells are usually present in the peripheral blood (Baseggio *et al*, 2004). EBV is often positive in the biopsies (in T or B cells) and serologically.

A number of autoimmune phenomena have been reported in association with AITL. These include autoimmune haemolytic anaemia (10-15%) (Brearley *et al*, 1979, Ruediger *et al,* 2006), vasculitis (Seehafer *et al*, 1980; Hamidou *et al,* 2001; Sugaya *et al,* 2001), polyarthritis, rheumatoid arthritis (Pieters *et al*, 1982; Pautier *et al*, 1999) and autoimmune thyroid disease (Ambepitiya, 1989; Pautier *et al*, 1999).

The clinical syndrome of AITL overlaps with a wide range of inflammatory and neoplastic processes, and the changes in peripheral blood and on bone marrow examination are usually non-specific. The diagnosis of AITL can only be achieved by

biopsy and histological examination of one of the enlarged lymph nodes, where characteristic morphological features can be best appreciated.

AITL shows prominent vascularisation by arborising venules, expansion of CD21+ follicular dendritic cell networks and the malignant T-cell population expresses CD4, 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 (Dogan *et al*, 2003). Cytogenetic findings (additional X, aberrations short arm of chromosome 1, trisomy 5) have prognostic significance in AITL (Schlegelberger *et al.* 1996). Molecular profiling shows a strong microenvironment imprint and overexpression of genes characteristic of normal follicular helper cells (de Leval *et al,* 2007).

7.3 Prognosis

Publications regarding the outcome and clinical management of AITL are limited because of the rarity of the disease. Most of the information is based on retrospective studies, small patient numbers and a limited number of case reports. The International T-cell lymphoma project (ITLP) included 243 patients with AITL and reported 5-year overall (33%) and failure-free (18%) survivals with median survival of less than 3 years, similar to patients with PTCL-NOS (Ruediger *et al*. 2006, Savage et al, 2004; Siegert *et al*, 1992; Pautier *et al*, 1999). Factors that were prognostic for outcome included the PIT (prognostic index for T-cell lymphoma; Gallamini *et al*. 2004) but not the IPI, age, B symptoms and performance status. Controlling for the PIT, a platelet count <150 x 10^9/l was prognostic for overall survival whereas B-symptoms were prognostic for failure-free survival (Ruediger et *al*. 2006). Based on the ITLP data an alternative prognostic Index for AITL (AIPI) has been derived, comprising: age > 60 years, PS ≥ 2, ENSs > one, B symptoms, and platelet count < 150 × 10(9)/L. Using the AIPI, the low-risk group (zero to one factors) had a 5-year survival of 44% compared to the high-risk group (two to five factors) with 5-year survival of 24%.
Gene expression profiles show a molecular signature with an important contribution from the follicular dendritic cells and other stromal components. Certain microenvironmental and immunosuppressive signatures are associated with poor outcome. (Iqbal *et al*, 2010a)

7.4 Treatment

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 alone. Patients often die from infectious complications which makes 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.

There have been reports of both single agent and combination chemotherapeutic regimens, such as CHOP, CVP (cyclophosphamide, vincristine, prednisone), VAP (vincristine, asparaginase, prednisone), steroids with or without cyclophosphamide, high-dose methylprednisolone, prednisone with or without COPBLAM

(cyclophosphamide, vincristine, prednisone, bleomycin, doxorubicin, procarbazine) or IMVP-16 (ifosfamide, methotrexate, etoposide) (Awidi *et al*, 1983; Siegert *et al*, 1992, 1995; Pautier *et al*, 1999; Gisselbrecht *et al*, 1998; Lopez-Guillermo *et al*, 1998; Pellatt *et al*, 2002). Although a complete remission rate of 50% can be achieved with combination chemotherapy, relapse rates remain high. Overall, combination chemotherapy appears to be superior to steroids alone (Pautier *et al*, 1999).
Other therapeutic approaches include low-dose methotrexate together with steroids (Gerlando *et al,* 2000), fludarabine (Ong *et al*, 1996; Hast *et al*, 1999; Tsatalas *et al,* 2001) and cladribine (Sallah *et al.*,1999). Gemcitabine (Sallah *et al*, 2001) can be beneficial, but again studies are based on a small number of patients, which does not allow statistically significant conclusions.
Interferon-alpha has been used for consolidation–maintenance therapy following conventional treatment to prolong chemotherapy-induced remissions by its differentiating, immunomodulating and antiproliferative effects (Feremans & Khodadadi, 1987; Hast & Gustafsson, 1991; Schwarzmeier *et al*, 1991; Siegert *et al*, 1991; Pautier *et al*, 1999). In the majority of patients, the remission duration is variable but is not longer than that observed with conventional treatments. Ciclosporin has also been given (Murayama *et al*, 1992; Advani *et al*, 2007; Takemori *et al*, 1999). This has a suppressive effect on the immune system, most notably on T cells, but also has a direct cytotoxic/apoptosis-inducing effect on lymphocytes. Its combined effects on neoplastic T cells may play an important role in the achievement of remission, but once again studies are limited to a few case reports.
Thalidomide has been used as an anti-angiogenic agent in a few patients, either following relapse or in refractory AITL, with promising results (Strupp *et al,* 2002, Dogan *et al*, 2005). Lenalidomide has also shown activity and there is a current trial in France evaluating CHOP+lenalidomide in AITL (REVAIL). Recently, it has been demonstrated that VEGF-A is expressed on both lymphoma cells and endothelial cells in AILT and that increased levels of VEGF-A were related to extranodal involvement and short survival time (Foss *et al.* 1997, Zhao *et al,* 2004). In a single case report complete remission was observed in a patient with AILT following bevacizumab (Bruns *et al.,* 2005). Phase II trials are in progress, including a study of CHOP + bevacizumab.
Monoclonal antibodies are being investigated in combination with chemotherapy. Case reports and small trials have shown responses to alemtuzumab (36% ORR), (Halene *et al, .*2006) diphtheria toxin fusion protein (denileukin difitox, ORR 50%) (Talpur *et al.,* 2002[a]; Foss *et al*., 2008) and to antibodies directed against CD2 or CD4; (Hagberg *et al.,* 2005). Many cases of AITL have a substantial infiltrate of CD20+ B-cells, providing a rationale for use of rituximab. Rituximab has being investigated in combination with CHOP chemotherapy by the GELA group (Joly *et al*, 2004). In 25 patients the 2 year PFS was 43% and OS 62% which was not thought to be superior to CHOP alone.

HSCT in AITL

Consolidation with auto-HSCT for patients in 1st CR or for chemosensitive relapse should be considered in suitable patients. It should be noted that use of fludarabine-containing regimens may hinder the ability to collect stem cells in some cases.
Rodriguez *et al* reported the outcome for patients with unfavourable prognostic factors at diagnosis, autografted upfront (15/19 patients) or as salvage therapy, with $\geq$60% patients alive and disease-free after 3 years (Rodriguez *et al*, 2007c). This approach has limited efficacy for patients with refractory disease or bone marrow involvement

(Schetelig *et al*, 2003; Rodriguez *et al*, 2007c; Mourad *et al*, 2008; Kyriacou *et al*, 2008).
The outcome of allografting patients with AITL has been assessed in a multi-centre retrospective study of 45 patients transplanted within the EBMT between 1998 and 2005 (Kyriakou *et al*, 2009**).** Twenty-seven patients were allografted in chemotherapy-sensitive disease, 18 were allografted in refractory disease and 11 had previously undergone auto-HSCT. RI-conditioning regimen were used in 20/45 patients. PFS was 53% and OS 64% at 3 years and was significantly better in chemotherapy-sensitive patients. A decreased relapse rate was observed in patients who developed cGVHD. This allo-SCT may be considered for young patients with multiple poor prognostic factors, ideally in the setting of a clinical trial.

7.5 Recommendations - AITL

- **The timing and selection of therapy depend on clinical presentation and prognostic features**
- **Patients requiring therapy should be entered into available clinical trials where possible**
- **Outside a clinical trial, CHOP or FC would be considered as standard therapies. (GRADE 1B)**
- **Immunomodulatory therapies such as steroids, ciclosporin, thalidomide and lenalidomide have some evidence of efficacy in chemo-refractory cases. (GRADE 2B)**
- **Consolidation with auto-HSCT should be considered for patients with chemosensitive disease in first remission or after relapse (GRADE 2B)**
- **Routine CNS prophylaxis is not warranted**.

8. Anaplastic Large cell lymphoma

The latest WHO Classification recognizes three distinct subtypes of anaplastic large cell lymphoma (ALCL): primary systemic anaplastic lymphoma kinase (ALK) positive, primary systemic ALK negative (provisional category) and primary cutaneous types, which have differences in immunophenotype, genetics, and clinical behaviour (Swerdlow et al, 2008). It is known that approximately 60% of systemic ALCLs are ALK positive (ALK-pos) and have a significantly superior survival to ALK-negative (ALK-neg) cases (ten Berge *et al*, 2000, Gascoyne *et al*, 1999), justifying the separation of these two categories. However, ALK- neg ALCL still has a better prognosis than PTCL-NOS (5year OS 49% v 32%). (Savage *et al*, 2008)
ALK is a receptor tyrosine kinase the expression of which is usually restricted to the central nervous system (Pulford *et al.,* 2001). 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. Fifteen different ALK-fusion variants have been identified. Gene expression profiles have shown distinct molecular signatures for ALK-pos and ALK-neg ALCL (Lamant *et al*, 2007). 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. (Piva *et al*, 2010)

8a. Anaplastic Large cell lymphoma (Alk-pos)

8a.1 Background, incidence and epidemiology

ALK-pos ALCL occurs at a young age (median age 30 years), accounts for approximately 3-5% of adult NHL and 30% of childhood NHL and shows a male predominance (Stein H *et al.,* 2000; Savage *et al.,* 2008). It must be distinguished from primary cutaneous ALCL. ALK-pos ALCL expresses CD30, t (2;5)/*NPM1-ALK* translocation, and variants, and clusterin (Nascimento *et al,* 2004). 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 (EBER and LMP1) (Brousset *et al.,* 1993).

8a.2 Presentation, diagnosis and staging

The majority of patients present with B symptoms (75%) and 75% present with Stage IV disease. (Savage *et al,* 2008). ALCL frequently involves both lymph nodes and extranodal sites (50-80%). Bulk disease or mesenteric involvement is unusual. The most common extranodal site is skin (21-35%), followed by bone (17%), soft tissue (17%), lung (11%), bone marrow (10%) and liver (8%). Involvement of the gut and central nervous system is rare (Stein *et al.,* 2000; Gisselbrecht *et al.,* 1998). Despite advanced stage and the involvement of multiple extranodal sites, the majority of patients fall into a low/low intermediate IPI risk category because of good performance status, younger age and a normal LDH.

8a.3 Prognosis

The most important prognostic indicator is ALK positivity, which confers a favourable prognosis with a 5-year FFS and OS of 70.5% and 58% compared to ALK-neg ALCL 49% and 36% respectively (excludes paediatric patients) (Savage *et al.,* 2008). In this prospective series, comparison of ALK-pos (n=16) and ALK-neg ALCL (n=23) patients with limited stage disease (defined as stage I or II, no B symptoms and non-bulky) failed to demonstrate a significant difference in FFS (p=.54) or OS (p=.21). The IPI is predictive of survival in ALCL (Savage *et al.,* 2004; Lopez-Guillermo *et al*, 1998; ten Berge *et al.,* 2003; Sonnen *et al.,* 2005). In the largest prospective series to date both the IPI and anaemia (Hb < 11.0 g/l) were effective in risk-group stratification in multivariate analysis (Savage KJ et al., 2008). Irrespective of ALK expression, B symptoms, high IPI, small cell variant histology and CD56 or survivin expression confer a worse prognosis (Suzuki *et al.,* 2000; Schlette *et al*., 2004). Mediastinal, visceral or skin involvement confer poorer prognosis (le Deley *et al,* 2008).

8a.4 Treatment

ALCL is a chemosensitive malignancy and has outcomes comparable to, or better than, IPI adjusted DLBCL following anthracycline chemotherapy. Trials reporting ALK-pos patients only are few. In a phase II trial of 53 patients a complete remission rate of 77% was reported with a DFS and OS at 10 years of 82% and 71% respectively (Falini *et al,* 1999). Good prognosis patients (IPI 0 or 1) had a 10-year OS of 94% compared with 41% in patients with a high/ high intermediate IPI score (IPI 3 or 4). In the only phase III trial including 91 patients the 5 year EFS was 70.5% and OS 49% at 5 years (Savage *et al.,* 2004). The retrospective review of patients treated within a number of German high-grade lymphoma trials suggested a benefit for the addition of etoposide for the younger patients (<60y) with ALCL histology. (Schmitz *et al*, 2010) The NCI used DA-EPOCH in a very small series (38 patients) where outcomes were particularly good for patients with ALK-pos ALCL with 5year PFS and OS in excess of 80% (Dunleavey *et al*, 2011). Therefore ALK-pos ALCL should be treated in adults with CHOP-like chemotherapy (with or without etoposide) as first line and platinum-based chemotherapy at relapse. Prognosis is so good in this group of patients that transplant should only be considered at relapse. ALCL patients autografted at relapse have a 67-100% 3-year EFS/PFS and a 78-100% 3-year OS (Jagasia *et al.,* 2004; Blystad *et al.,* 2001; Song *et al.,* 2003).

Very successful results are achieved in paediatric series (Seideman *et al.* 2001). It is likely that such regimens will be tolerable across the teenage and young adult age group up to at least 24 years. Though not proven, it is likely that by analogy with the emerging data in acute lymphoblastic leukaemia (Stock *et al,* 2008) this may be the optimum strategy for the patients in the younger age group. Though the prognosis of this disease in young people is in general better than that of other T-cell subtypes it is also important to note that there are patients with very adverse prognostic features (e.g. peripheral blood involvement) who will probably benefit from more intensive inpatient chemotherapy schedules.

Several different unconjugated antibodies directed at the CD30 antigen (a member of the TNF receptor superfamily) have been studied in phase II trials in patients with refractory or recurrent ALCL and show responses in up tp 20% of individuals (Forero-Torres *et al.,* 2009; Ansell *et al.,* 2007). *In vitro* data indicate that anti-CD30 antibodies

activate NF-κB and sensitise the malignant cells to chemotherapy agents (Cerveny *et al.,* 2005). Higher affinity and fully humanised CD30 antibodies (Hammond *et al.,* 2005) are in phase I trials. However, the most exciting development in the treatment of relapsed ALCL has been the introduction of the anti-CD30 antibody-drug conjugate brentuximab vedotin. This delivers a potent antimicrotubule agent directly to CD30+ cells. In a Phase II trial in 58 patients, 86% achieved an objective response, with 57% CRs. Median duration of OR was 12.6 months.(Pro *et al,* 2011) Tolerability was good with cytopenias and peripheral sensory neuropathy as the major side effects. A number of patients were able to proceed to consolidation with autologous or allogeneic HSCT. On the basis of these results brentuximab vedotin has been approved in US and Europe and is now undergoing front-line studies in combination and in randomised comparison to standard CHOP.
Other agents have been explored but without such compelling data. These include: daclizumab (CD25 antibody) (Linden 2004; Grigg *et al.,* 2006),and humanised anti-CD4 (zanolimumab). ALCL overexpresses the Heat shock protein 90 (HSP90), which has been shown to chaperone NPM1-ALK. *In vitro* HSP90 inhibition induces apoptosis further enhanced by conventional chemotherapy (Georgakis *et al.,* 2005). Other developmental approaches include targeted inhibition of NPM1-ALK which has been shown *in vitro* to cause ALCL- specific growth inhibition which can be augmented by chemotherapeutic agents (Hsu *et al.,* 2007; Christensen *et al,* 2007). Tumour vaccines targeting the ALK protein are also in development (Passoni *et al.,* 2003, Ait-Tahar *et al*, 2006, Piva *et al,* 2006).

8b. Anaplastic Large cell lymphoma (ALK-neg)

ALK-neg ALCL is less well characterised and it is still unclear if this should be classified as a separate entity. It is difficult to diagnose since, unlike ALK-pos ALCL, there is no specific marker and histologically there is overlap with PTCL-NOS and with Hodgkin lymphoma. Genetic tests can be powerful in identifying ALK-neg ALCL but are not yet widely available (Agnelli *et al,* 2012). The peak age incidence is 40-65 years with no gender preponderance. Extranodal involvement is less common than in ALK-pos ALCL. Morphologically it is indistinguishable from ALK-pos ALCL but EMA expression is more variable, 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 since the outcomes are less good it is recommended that the standard management should become the same as that for PTCL-NOS. Most cases are CD30+ and therefore responsive to brentuximab vedotin as stated above.

8c. Primary Cutaneous Anaplastic Large cell lymphoma (ALK-neg)

This is typically seen in older men as a solitary asymptomatic cutaneous or sub-cutaneous 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, and a review of 146 cases showed a 10-year survival of 95% (Willemze *et al,* Blood 2005). Multi-focal skin lesions, especially those sited on the leg, appear to have a poorer prognosis. Treatment is directed at local control with excision and/or radiotherapy and patients may be successfully re-treated. Aggressive treatment should be avoided although chemotherapy may be indicated if there is systemic disease.

8d Primary anaplastic large cell lymphoma associated with breast implants

Over 40 cases of ALCL limited to the breast have been reported in the literature, occurring in association with saline or silicone implants.(Popplewell *et al,* 2011) The estimated risk is low at 1:50,000 to 1:100,000. There is strong evidence for a causative link. Patients usually present with an effusion associated with the implant, which develops after a median of 7 years (range 1-23 years). The effusions are either seroma-associated with malignant cells only present in the fluid or tumour-associated where there is a distinct tumour infiltration (lump). The tumour cells are CD30+ and monoclonal. Treatment is usually with surgical removal of the implant and associated tumour followed by radiotherapy+/-chemotherapy. The rarity of the condition makes it impossible to determine the correct treatment but the behaviour is thought to be indolent, particularly for the seroma-associated type wher radiotherapy alone may be sufficient, whilst the tumour-associated type may merit a more aggressive treatment approach.

8.5 Recommendations - ALCL

- **The International Prognostic Index has predictive value in ALCL but ALK positivity is the most important prognostic factor.**
- **Patients with limited stage anaplastic large cell lymphoma and no adverse prognostic features by IPI should be treated with 3-4 cycles of CHOP chemotherapy and involved field radiotherapy.**
- **All other patients should be entered into a clinical trial or receive 6-8 cycles of CHOP chemotherapy. (GRADE 1A)**
- **ALK-neg ALCL should be treated as for PTCL-NOS**
- **Primary cutaneous ALCL (ALK-neg) should be managed with local excision +/- radiotherapy and chemotherapy reserved for those patients with systemic disease**
- **At relapse patients should receive platinum-based chemotherapy or an alternative salvage regimen such as brentuximab vedotin and patients with chemosensitive disease should be considered for transplant**

III. Extranodal PTCL

9. Extranodal NK/T-cell lymphoma, nasal type

9.1 Background, incidence and epidemiology

This is an aggressive, largely extranodal lymphoma, usually of NK-cell type (CD2+, CD56+, CD3ε+), but with recognised T cell phenotypic variants. It is almost invariably EBV- associated and often presents as localised disease in and around the nasal structures. This and a poor survival earned it the historical term 'lethal midline granuloma'.

These are very rare tumours in the Western world but are commoner in Asia and South America. Among 1153 new adult cases of PTCL studied in the ITLP there were 136 cases of extra-nodal NK/T cell lymphoma (nasal 68%, extranasal 26%) (Au *et al,* 2009). The disease frequency was higher in Asian countries with no differences in age, gender or immunophenotypic profile between nasal and extranasal cases. In one large Japanese analysis 40 out of 1000 lymphomas were found to conform to the NK/T subtype (Miyazato *et al,* 2004). They are seen mainly in adult males (median age 50-60 years; M:F ratio 3:1) and, perhaps in relation to their EBV-association, have been reported in the setting of immunosuppression / post transplantation. EBV is a constant finding, particularly in the cases presenting as localised nasal disease and it is assumed that the virus is involved in the pathogenesis (Harabuchi *et al,* 1996). EBV positivity is also seen in aggressive NK cell leukaemia (covered under the leukaemia section) and, in some but not all cases, the latter represents the leukaemic counterpart of extranodal NK/T cell lymphoma. However, EBV positivity is also seen sporadically in other T-cell lymphomas and is therefore not exclusive in defining the NK/T cell diseases.

9.2 Presentation, diagnosis and staging

The condition almost invariably presents in extranodal sites, classically in the nasal structures but nodal disease is occasionally seen and secondary nodal spread is not uncommon. Three clinical patterns are recognised: disease involving the nose, naso-pharynx and upper aero-digestive tract; disease involving another extra-nodal site, commonly skin, gut or testes and a disseminated form with widespread tissue infiltration and BM involvement with occasional leukaemic phase causing overlap with aggressive NK-cell leukaemia. Blood and marrow tend not to be involved in the more localised extra-nodal disease forms (Vose *et al*, 2008; Kim *et al*, 2008) Disease occurring outside the nasal cavity is more aggressive with short survival times and poor response to therapy.

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. Extension and invasion into the orbits, sinuses and oral cavity occurs and dissemination is frequent, usually to regional nodes (Li *et al,* 2009). Widespread extranodal disease, with or without nasal involvement, is usually associated with systemic symptoms. (Kwong,2005). An association with the haemophagocytic syndrome has been reported (Kwong *et al,* 1997).

CNS involvement is uncommon (5-10%). It has been reported by direct extension and in one case as a primary, isolated intracerebral lesion (Kaluza *et al,* 2006) but there is no good evidence to support routine examination of the CNS or prophylactic therapy. Diagnosis and staging is no different in principle to that for PTCL-NOS (see above) but EBV should be routinely demonstrated in the biopsy material and staging investigations should be aimed at demonstrating disease in orbit, skin, gut, testis and viscera as well as nodal areas. Tissue biopsies often contain necrotic material making precise diagnosis difficult and material should be reviewed by expert haemato-pathologists. Furthermore, the TCR is not rearranged giving no suitable test for confirmation of clonality. Whether conventional staging is clinically valid and useful in this condition is debatable. 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 (Matsue *et al,* 2009). The main distinction is between those cases presenting with localised disease (stage I/II) and those with more advanced stage – usually with multiple extranodal sites of involvement (Chim *et al,* 2004; Chan *et al,* 1997). This is clinically important because of the apparent sensitivity of the tumour to radiation and the relative insensitivity to chemotherapy. Localised disease is thus quite curable with radiotherapy but disseminated disease does poorly.
Genome –wide array-based comparative genomic hybridisation and gene expression profiling (GEP) have identified differences in patterns of gene alteration between aggressive NK-cell leukaemia and extranodal NK/T cell lymphoma (Nakashima *et al*, 2005) and between NKTCL and other PTCL (Huang *et al*, 2010). These have shown perturbations in angiogenic pathways and platelet derived growth factor receptor (PDGFRA), and have identified novel tumour suppressor genes. (Iqbal *et al*, 2009) A subset of γδPTCL-NOS were found to be very similar to NKTCL by GEP and distinct from hepatosplenic T-cell lymphoma. (Iqbal *et al,* 2010b)

9.3 Prognosis

These tumours are very aggressive with destructive local invasion. The rarity makes accurate figures hard to assess for outcome but it seems clear that disseminated disease has a very poor prognosis, while cure is possible in localised presentations (Chim *et al,* 2004; Chan *et al,* 1997). Survivals (at 5 years) range from 20% to 35% in different series but most of the cases included in these figures are localised stage I/II nasal presentations and when considered separately, the patients with disseminated disease almost all die, mostly within a few months (Chan *et al,* 1997). Five-year OS for extra–nasal disease is reported as 9% compared to 42% for localised disease. This is consistent with the more recent report from the ITLP of median OS for nasal cases of 2.96 years compared to extra-nasal of only 0.36 years (Au *et al*, 2009). Localised, nasal-type disease is therefore amenable to cure, if only for a minority, but the disseminated cases remain a very considerable challenge.

The IPI is valid only in the sense that a low score is seen in localised 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* (2006) have developed a prognostic model which includes 4 risk factors: B symptoms, advanced stage, 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.

Other unfavourable prognostic factors include bone or skin involvement, expression of p19 (Bossard *et al,* 2007), Ki67> 50%, elevated C reactive protein (CRP), anaemia, thrombocytopenia (Au *et al*, 2009) and high serum EBV DNA levels (Kim *et al,* 2009) and EBV+ cells in the BM. EBV quantification is helpful for assessing the tumour load and prognosis at diagnosis and also for monitoring response and relapse. A high Ki 67 may have prognostic significance in localised disease.

Prognosis has improved in recent years due to the introduction of early radiotherapy.

9.4 Treatment

There are no trials randomising different options in this disease. Most reports consist of between 15 and 100 patients, usually retrospective and almost all from the geographical areas in which this tumour is prevalent. It is not therefore possible to give clear guidance as to optimal therapy. Most authors have used radiotherapy +/- anthracycline-based chemotherapy. High dose therapy has been investigated but only in small numbers and not systematically (Kim *et al,* 2006, Au et al, 2003). A summary of the available data suggests that the tumour is not very chemosensitive, with low CR rates to CHOP/CHOP-like schedules and frequent failures during chemotherapy (Chim *et al,* 2004; Chan *et al,* 1997). It has been suggested that p-glycoprotein expression by the tumour may mediate this drug resistance but the literature is contradictory (Egashira *et al*, 1999, Kim *et al*, 2004; Huang *et al*, 2009). Involved field radiotherapy (IFRT) produces excellent initial control and it is the patients with stage I/II disease who have received IFRT +/- chemotherapy who make up most of the survivors. In one retrospective analysis of 79 patients for example, progression during chemotherapy was seen in around half of cases and 9 of 17 patients progressing loco-regionally achieved a CR with IFRT, underlining the disappointing results with standard chemotherapy and the utility of irradiation (Cheung *et al*, 2002). A retrospective review of 105 patients in China showed 5 year PFS and OS of 61% and 66% for primary radiotherapy compared to 66% and 76% for combined modality therapy, suggesting that chemotherapy may add little benefit for localised disease (Li et al 2006). Huang et al (2008) in a study of 82 patients with localised disease showed that early radiotherapy was the only independent prognostic factor and that 5-year OS was significantly better for those patients receiving >54 Gy. The consensus is that radiotherapy dose should exceed 46 Gy, and that the optimal dose is 50 Gy, delivered to the nasal cavity plus the sinuses. Concurrent chemotherapy may improve both local and systemic disease control. Two recent reports of chemoradiotherapy for localised (Stage IE to IIE) showed improved results compared to historical controls of radiotherapy alone (Kim *et al*, 2009; Yamaguchi *et al*, 2009). In both trials the chemotherapy regimens contained dexamethasone, etoposide, ifosfamide and cis- or carbo-platin.

Aviles et al (2007) reported 61 patients in Mexico, all of whom had disease that was not localised to the nasal region (i.e. a high risk group). They were treated with a regimen of cyclophosphamide, methotrexate, etoposide and dexamethasone with radiation sandwiched between cycles 3 and 4 of 6 cycles. They reported a response of 49/61

CRs and 12 'failures'. Those who failed and 9 of the CRs that relapsed, died of disease with an OS at 5 years calculated to be 65%.

A number of authors have reported the use of chemotherapy regimens/agents other than CHOP (Au, 2010). The most published is L-asparaginase, alone or in combination with other agents (e.g. the SMILE regimen containing dexamethasone, methotrexate, ifosfamide, l-asparaginase and etoposide). Most of this data is in relapsed or refractory disease and responses of around 50% with 5-year OS of 65% (86% limited stage, 38% advanced) are quoted with impressive outcomes compared to the historical results from CHOP-like salvage (Yamaguchi *et al,* 2008, Yong *et al,* 2006, Jaccard *et al,* 2011, Obama et al, 2003). A recent prospective trial of the SMILE regimen in 38 patients with good PS and satisfactory blood counts, liver and renal function, reported an ORR of 79% (Yamaguchi *et al,* 2011). The same SMILE regimen has also been evaluated in 43 newly diagnosed and 44 relapsed/refractory patients where the entry criteria were not so stringent. (Kwong *et al,* 2012) The ORR was similar at 81% (CR 66%) and did not differ between newly diagnosed and relapsed patients. Toxicities, particularly haematological, were significant. The 5 y OS was 50% and 4y DFS 64%. IPI was the most significant factor impacting on outcome. Low EBV copy number (by PCR) was predictive of better response to SMILE. These results are the best seen with any therapy in this disease group. No formal comparisons with CHOP have been made. Nonetheless, the uniformly poor results with CHOP (arguably adding little to radiotherapy) suggests that an asparaginase-containing approach may be justified in disseminated disease and worthy of consideration in both newly diagnosed and relapsed/refractory settings. Care needs to be taken regarding the specific toxicities associated with asparaginase use, particularly clotting abnormalities.

Exploration of other novel agents in this disease, including the use of EBV-specific lymphocytes, is attractive and should theoretically be trial-based as conventional therapy is inadequate. In the UK this will only be possible by inclusion in trials for other T-cell lymphomas as there are insufficient cases to expect a specific study to emerge. In the absence of a trial, localised disease should certainly receive radiotherapy, which offers very good control and a reasonable prospect of cure. There is little evidence to support the addition of CHOP-based chemotherapy (You *et al,* 2004). The use of agents which bypass P-glycoprotein is preferable. Such combination regimens might include asparaginase, methotrexate, ifosphamide, etoposide and steroids. Gemcitabine –based treatment may also be effective. Asparaginase-containing regimens should be considered by the treating multi-disciplinary team (MDT) as a rational, but unproven alternative to CHOP in 1st line and with more robust rationale in 2nd line therapy.

9.5 Recommendations - Extranodal NK/T-cell lymphoma

- **Diagnosis and staging uses the same investigations and techniques as for PTCL-NOS (see above). Demonstration of EBV virus in the biopsy is important diagnostically.**

- **Assigning a conventional IPI score is of limited value as most cases are localised and have a low score, yet the survival is still poor (GRADE 1B)**
- **The distinction at diagnosis between localised disease and disseminated disease is important as the latter has a dismal prognosis and might be considered for experimental therapy as first line if available (GRADE 1B)**
- **Assessment of EBV by PCR can be helpful in monitoring disease and may have prognostic relevance**
- **Outcome is unsatisfactory with CHOP-like therapy and entering patients into relevant clinical trials if available is recommended.**
- **Patients with localised disease should receive radiation with 50-55 Gy (GRADE 1B)**
- **The value of additional chemotherapy (CHOP, etoposide-based or asparaginase-based) for local disease remains unclear but is considered conventional pending more information (LEVEL GRADE 1B)**
- **Asparaginase-containing regimens should be considered in disseminated first-line and in relapsed or refractory disease (GRADE 1B)**
- **High dose therapy is unproven and there is no basis to recommend it outside a trial**

10 Enteropathy-Associated T-cell lymphoma (EATL)

10.1 Background, incidence and epidemiology

This is an 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 outcome is poor, partly due to the biology of the disease and partly because of the poor performance status of patients in the setting of malabsorption and malnutrition.

EATL is extremely rare in most parts of the world but seen more commonly in Northern Europe, where coeliac disease is relatively frequent. In the UK the annual incidence was 0.14/100,000 in one study (Sieniawaski *et al,* 2010). Patients may have a history of coeliac disease or can be shown to have histological evidence of it at the time the lymphoma is found. Most cases are adult onset, rather than evolving in patients known to have had coeliac from childhood. There is a complex relationship between overt EATL and the various stages of coeliac disease. It seems likely that the tumour arises from abnormal intra-epithelial lymphocytes and the refractory phases of coeliac disease (RCD) are characterised by the accumulation of such aberrant cells, which may be clonal and share genetic and phenotypic similarity to subsequent EATL lesions. In this sense, some cases of RCD (RCD type II) may be regarded as a part of the spectrum of intestinal T-cell lymphoma or a form of 'in situ' EATL (Cellier *et al,* 2000). EBV+ intestinal T-cell lymphomas are primarily nasal-type NK/T cell lymphomas and not EATL. Similarly, other T-cell lymphomas such as ALCL and hepatosplenic T cell lymphoma may present with intestinal disease and should not be confused with this rare entity.

10.2 Presentation, diagnosis and staging

The typical patient is an older (median age 57 years) male presenting with diarrhoea and abdominal pain. A minority of patients already known to have coeliac disease, progress clinically through a phase of worsening malabsorption terminating in overt bowel lymphoma with ulceration, obstruction or perforation. Others develop the latter features acutely with no history (Gale *et al,* 2000). The sites of involvement are usually jejunum or ileum – often with multiple, ulcerative lesions. Rare cases are seen in the stomach or large bowel and it has been described outside the gastro-intestinal tract. There may be associated dermatitis herpetiformis and hyposplenism.

The diagnosis is made from bowel histology. Staging should include the routine examination of bone marrow and whole body CT scanning. These generally show no disease outside the GI tract but dissemination can occur and should be documented. The more challenging aspect is how to image, biopsy or survey the GI tract at diagnosis and during follow up. Multiple lesions often occur. CT scanning can show these lesions and also some of the characteristic features of the different stages of coeliac disease in the bowel (Mallant *et al,* 2007). The commonest site of presentation is in the small bowel, which is relatively inaccessible. Histology from distant sites at diagnosis

often shows increased intra-epithelial lymphocytes, which as mentioned above may or may not share an aberrant phenotype and clonal relationship to the tumour cells. These features argue for close liaison with a gastroenterologist experienced in managing coeliac disease to guide imaging and biopsy at diagnosis and to assist in follow up and the nutritional care of the patient.

10.3 Prognosis

This is very poor in all reported series, with median PFS 3.4 months and OS 7 months (Sieniawski *et al,* 2008). Accurate figures are precluded due the rarity of the disease but are of the order of 10% disease free survival at 5 years (Gale *et al,* 2000). In the ITLP there were 62 patients identified with EATL (4.7%) who had a 5-year FFS of 4% and OS of 20%. There are clearly some long-term survivors so it is reasonable to aim for curative therapy in suitable patients. Even though most patients have localised (stage I – IIE) disease, their performance status is usually poor due to the GI tract problems discussed above and conventional IPI assignment is unhelpful as there is no good risk group in this disorder and no rationale for different therapeutic strategies at diagnosis.

10.4 Treatment

There are no satisfactory therapies for this condition. The rarity of the disease has hampered assessment of novel or experimental therapies. Conventional lymphoma treatment (CHOP-based chemotherapy) yields responses in 50% or more of cases but long term survival in no more than 10%. Alternative, more intensive therapy has not been clearly shown to be superior (Wohrer *et al,* 2004). The data regarding autologous stem cell transplantation, while promising, is limited and requires confirmation (Bishton & Haynes 2007). Interestingly, there are reports of such dose intensification approaches in RCD type II, with evident clinical response. Whether this delays or reduces the risk of subsequent EATL is unknown (Al-toma *et al,* 2007).

The Scottish and Newcastle Lymphoma group (SNLG) in the UK have piloted an intensive approach involving salvage-type chemotherapy: CHOP for 1 cycle followed by IVE (ifosfamide, etoposide, epirubicin) for 3 cycles alternating with intermediate- dose methotrexate and up-front autologous transplantation. Compared to historical controls treated with CHOP-like chemotherapy alone, there was a better CR rate (72% v 42%), 5-year PFS (56%v 20%) and 5-year OS (67%v 22%) for those treated with the intensive regimen (Sieniawski *et al,* 2010). This approach has been adopted in a recently approved NCRI trial. Alternating IVE and high dose methotrexate (HDMTX) (but without initial CHOP) was also used with good effect pre-autograft in the Bishton and Haynes study (2007). A retrospective review by the EBMT of 44 patients with EATL who received an autograft between 2000 and 2010 showed a relapse rate of 39%, PFS of 54% and OS of 59% at 4 years. (Jantunen *et al,* 2013) Better outcomes were seen if patients were transplanted in 1st remission confirming the value of this strategy when used early.

In summary, this is a rare disease, making clinical trials of new agents very difficult. Conventional chemotherapy gives poor results but there are some long-term survivors. Treatment is complicated by poor nutrition and a significant risk of bowel perforation. Dose intensification is often attempted but is yet to be confirmed as beneficial in adequate trials and must be seen as experimental.

10.5 Recommendations – EATL

- **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 (GRADE 1C)**
- **Assigning a conventional IPI score is of limited value as there is no good prognostic group and most cases are stage I-IIE.**
- **If there are trials available at the time of diagnosis, entry should be strongly considered as there is no satisfactory standard therapy.**
- **CHOP-like therapy, with or without an up-front autograft remains a common approach outside a trial and adoption of a more intensive approach such as the NCRI/SNLG protocol is a reasonable option in fitter patients (GRADE 2B)**
- **Nutrition is a major issue in managing these patients and dietetic/gastroenterology advice is essential at all stages of treatment and follow-up (GRADE 1C)**

11 Hepatosplenic T-cell lymphoma

11.1 Background, Incidence and epidemiology

This is a rare entity, mainly affecting adolescent or young adult males. . It is a distinctive and aggressive disease with a characteristic presentation and clinical course. It may be seen following solid organ transplant and in other situations of immunosuppression (Belhadj *et al,* 2003). There is no association with EBV. Most cases show a characteristic phenotype, expression of the $\gamma\delta$ T-cell receptor, and have an isochromosome 7q abnormality (Vega *et al,* 2007). A variant expressing the $\alpha\beta$ T-cell receptor is well described (Macon *et al,* 2001).

11.2 Presentation, Diagnosis and staging

This is a systemic, extranodal disease involving the liver, spleen and bone marrow (Weidmann *et al,* 2000). Lymphadenopathy is a rare finding. The marrow involvement causes cytopenias, thrombocytopenia being the most common (Cooke *et al,* 1996; Macon *et al,* 2001; Vega *et al,* 2007). The median age at diagnosis is 34 years.
The diagnosis is made from the above features along with typical histology showing sinusoidal infiltration with tumour cells in the affected tissues. The phenotype is characteristic as mentioned above. CT scanning adds little. Staging and assignment of risk group is irrelevant as this is a distinctive clinico-pathological entity presenting as stage IVB, high-risk lymphoma in almost every case.

11.3 Prognosis

The outlook is very poor, with only occasional survivors reported in the few, small series in the literature. Two survivors out of 21 patients were reported by Belhadj with an overall median survival of 16 months (Belhadj *et al,* 2003) and in another series the median was less than 1 year for a group of 9 patients (Cooke *et al,* 1996) 14 variant $\alpha\beta$ T-cell receptor cases were reported in a further paper with very few survivors (Macon *et al,* 2001). The reports comment on the use of standard and salvage chemotherapy in these cases.

11.4 Treatment

It is clearly impossible to base guidance on the inadequate data in this rare condition and the literature paints a grim picture regarding response to conventional chemotherapy. There are a number of case reports concerning treatment with pentostatin (Grigg *et al*, 2001, Iannitto *et al*, 2002, Corazelli *et al*, 2005), alemtuzumab, alemtuzumab + a purine analogue (fludarabine, pentostatin or cladribine) (Mittal *et al,* 2006; Jaeger *et al*, 2008) and allogeneic-HSCT (Konuma *et al*, 2007). All that can be said is that responses have been seen with these approaches and perhaps some patients remain alive post allograft (Chanan-Khan *et al,* 2004; Domm *et al,* 2005; He *et al,* 2007; Sakai *et al*, 2006). The same can, however, be said of conventional CHOP-like therapy or a platinum-cytarabine based regimen (Belhadj *et al,* 2003), from which there has been the occasional survivor as mentioned in the series above. Purine analogues may have some selective effect judging from cell line studies (Aldinucci *et al*, 2000). It seems reasonable to seek trial therapy for patients where available as there is no evidence-base from which to recommend any form of standard treatment and the great majority of cases are fatal.

11.5 Recommendations - Hepatosplenic T-cell lymphoma

- **No satisfactory recommendations can be made from the limited evidence base.**
- **Trial or experimental therapy should be considered if available**
- **Allogeneic bone marrow transplantation could be considered but the evidence is purely anecdotal**
- **Conventional chemotherapy approaches as for PTCL-NOS are the default and there are some survivors reported in the literature (GRADE 2C)**

12 Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)

12.1 Background, Incidence and epidemiology

This is one of the rarest defined forms of PTCL with only 0.9% of cases in the ITLP (Vose *et al*, 2008) .It presents as subcutaneous tumour nodules. It can be seen at any age, including in children, (median 36 years, M:F ratio 2:1 (Willemze *et al,* 2008). EBV is absent and there appears to be no obvious geographical variation. Two subtypes were previously recognised, based on T-cell receptor expression: the larger group had a CD8+ve, CD56- phenotype with an $\alpha\beta$ T-cell receptor, the remainder were composed of $\gamma\delta$ T cells with a CD8- CD56+ phenotype (Willemze *et al*, 2008) This latter group appear to have a relationship to immunosuppression, and a significantly poorer prognosis. In the new WHO classification these cases have been re-defined as primary cutaneous $\gamma\delta$ T-cell lymphomas (Arnulf *et al,* 1998; Salhany *et al,* 1998; Swerdlow *et al*, 2008).The term SPTCL is now therefore restricted to those cases with an $\alpha\beta$ phenotype.

12.2 Presentation, Diagnosis and staging

Presentation is typically with multiple, indurated, subcutaneous nodules up to a few centimetres in size and ulceration is uncommon. Lesions may be solitary. Some cases have an indolent prodrome with recurring and self-healing lesions (Papenfuss *et al,* 2002). 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. There is an association with the haemophagocytic syndrome, which may be a presenting feature (Go *et al,* 2004). The primary cutaneous $\gamma\delta$ T-cell lymphomas are more closely associated with haemophagocytosis and this adds further weight to their separate classification. (Hoque *et al,* 2003; Go *et al,* 2004). The diagnosis is made from biopsy material showing involvement of the fat and subcutaneous tissue with sparing of the overlying skin layers. It is important to stage the patient fully as localised presentations may have a relatively good prognosis.

12.3 Prognosis

This was generally held to be poor but there is conflict in the literature and reports may well have been discussing more than one disease with differing outcomes. SPTCL ($\alpha\beta$ T-cell receptor expressing disease) with tumour localised to the subcutaneous tissues, can behave in an indolent way in some patients and may respond well to conventional chemotherapy with good overall outcome (Massone *et al,* 2004; Papenfuss *et al,* 2002; Salhany *et al,* 1998 Willemze *et al*, 2005). The prognosis is therefore not uniform. One literature review summarised the outcome for 156 patients (treated differently) and showed that 48% of them had died of disease at 2 years (Go *et al,* 2004). The inferior outcome for cases with a $\gamma\delta$ phenotype was again noted. An EORTC report of 83 cases reports a significant difference in 5-year OS for the $\alpha\beta$ and $\gamma\delta$ subtypes and also notes the significance of a haemophagocytic syndrome (HPS) as a strong adverse prognostic factor. 5-year OS was 91%, 46% and 11% respectively for the $\alpha\beta$ type without HPS, $\alpha\beta$ type with HPS and $\gamma\delta$ subtypes with or without HPS. This supports the decision to

remove the γδ subtypes from this diagnostic category and underlines the impact of HPS in the αβ expressing cases. (Willemze *et al,* 2008).

12.4 Treatment

There are no significant published studies of uniform treatment, only case reports and retrospective, clinico-pathological surveys in which differing therapies are mentioned. It is therefore not possible to compare treatments. One or two points recur in the literature and are worthy of note. Disease control with steroids or radiotherapy is possible initially. Not all cases behave aggressively and given the reports of self-healing lesions and indolent behaviour in some patients, it may be reasonable to manage localised disease with local therapy and close observation, particularly in older or less fit patients. Outcomes with a mixture of observation, steroids, single agent chemotherapy and conventional CHOP-like chemotherapy (depending on the age and stage of the patient group in the reports) range from 30-91% (Go *et al,* 2004; Willemze *et al,* 2008). Small numbers of patients are reported to have done well at relapse with autograft strategies. It is impossible to comment on whether intensification of therapy up-front would be of value. The re-definition of this entity to include only αβ-expressing cases in the recent WHO classification seems highly clinically relevant and these patients may have a better prognosis than was previously thought.

12 5 Recommendations - SPTCL

- **No conclusive recommendations can be made from the limited evidence base. The cases described in the literature are not uniform**
- **This is not a universally aggressive disease and careful initial assessment and observation should be undertaken before committing to treatment (GRADE 2C)**
- **CHOP-like chemotherapy appears to be effective and produces survivors (GRADE 2C)**
- **Relapsed disease may respond to dose intensification in some patients (GRADE 2C)**
- **Local radiotherapy has a place for good prognosis localised symptomatic skin involvement which does not resolve with topical steroids (GRADE 2C)**

Summary of Recommendation

Diagnosis and staging

- **Diagnosis requires expert examination of tissue including a detailed phenotypic assessment. Clonality should be assessed by PCR for TCR gene rearrangements. This is the subject of a separate BCSH guideline.**
- **Staging should include blood, bone marrow and radiology as well as assessment of performance status and prognostic factors to allow assignment of a prognostic score and planning of therapy**
- **Lumbar puncture/MRI of brain is not routinely required in the absence of CNS symptoms or signs.**
- **PET scanning is not established in the routine staging of PTCL**
- **The T-cell malignancies are rare and often complex diseases. Diagnosis and management should be discussed in a network multi-disciplinary team meeting and those patients requiring treatment should generally be referred to a cancer centre or tertiary centre with specialist expertise.**

Prognosis

- **The IPI gives useful prognostic information in PTCL and should be calculated, but it clusters many cases in the higher risk groups**
- **Newer T-cell specific prognostic scores appear to be more discriminatory and may be valuable in prospective trials**

1. T-Prolymphocytic Leukaemia (T-PLL)

- **Intravenous alemtuzumab should be used as first line therapy for T-PLL. (GRADE 1B)**
- **Patients failing to respond should receive the combination of alemtuzumab plus pentostatin or another purine analogue (GRADE 1C)**
- **All eligible patients should proceed to either autologous or allogeneic stem cell transplant in first remission. (GRADE 1C)**
- **Patients should be entered into clinical trials wherever possible**

2. T-Large Granular Lymphocytic Leukaemia (T-LGL)

- **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 (<9 g/dl) and/or the need for transfusion; severe neutropenia (< 0.5 x10^9/l) associated with infection; severe thrombocytopenia (< 50 x 10^9/l); or any combination of these.**
- **Oral ciclosporin or weekly oral low dose methotrexate (10 mg/m^2/week) are effective in more than 75% of cases (GRADE 1B)**

- **Responses may be enhanced by the use of growth factors (erythropoietin and/or GCSF) (GRADE 1B)**
- **Second line treatments include purine analogues (pentostatin), cyclophosphamide and alemtuzumab (GRADE1B)**

3. <u>Chronic Lymphoproliferative disease of NK cells (CLPD-NK)</u>

- **management same as for T-LGL**

4. <u>Aggressive NK-cell Leukaemia</u>

- **Rare aggressive NK- cell leukaemias occurring in younger adults require a different therapeutic approach and consideration of stem cell transplantation (GRADE 2C)**
- **Patients should be entered into clinical trials wherever possible**

5. <u>Adult T-cell Leukaemia lymphoma (ATL)</u>

- **Exclude co-infection with strongyloides prior to commencing therapy. Appropriate antimicrobial prophylaxis during therapy should be instituted for seropositive patients.**
- **Smouldering & Chronic**
    - **no benefit from early chemotherapy therefore watch and wait**
    - **Zidovidine (ZDV) + Interferon-α +/- monoclonal antibodies may be considered (especially in chronic ATL) in the context of a clinical trial (GRADE 1B)**
- **Lymphoma type**

  - Induction with CHOP or alternative multi-agent regimen plus G-CSF (GRADE 1B) with Concurrent ZDV + Interferon-α (GRADE 1B)

  - ZDV + Interferon-α maintenance +/- Monoclonal antibodies (MoAbs) OR Allogeneic transplant in 1st CR for eligible patients (GRADE 2C)
- **Leukaemia (Acute) type**

  - Induction with anti-retoviral therapy alone (ZDV + Interferon-α OR Induction with CHOP or alternative multi-agent regimen plus G-CSF (GRADE 1B) + Concurrent ZDV + Interferon-α

  - Allo HSCT in 1st CR for eligible patients (GRADE 1B)

  - OR ZDV + Interferon-α maintenance +/- MoAbs (GRADE 2C)

  - OR consolidation with novel agents e.g. Arsenic trioxide, αIFN; proteasome inhibitor in clinical trials
- **CNS prophylaxis should be considered using the same criteria as for diffuse large B-cell NHL (GRADE 2C)**

6. <u>Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)</u>

- **Primary treatment should be within the context of a clinical trial if possible a standard therapy gives disappointing results (GRADE1B)**

- **Outside trial, CHOP remains the standard therapy. Consideration should be given to consolidation with auto-HSCT (GRADE 2B)**
- **Relapsed or refractory disease should be treated with relapse-schedule combination chemotherapy and considered for Allo-HSCT with reduced intensity conditioning (GRADE 2B) or autologous stem cell transplantation (GRADE 2B) or novel therapies within a trial setting**
- **Outside a trial a number of agents show promise, particularly gemcitabine, bendamustine, praletrexate and romidepsin but the data are insufficient to recommend routine use.**
- **CNS prophylaxis should be considered using the same criteria as for diffuse large B-cell NHL (GRADE 2C)**

7. Angio-immunoblastic T cell lymphoma

- **The timing and selection of therapy depend on clinical presentation and prognostic features**
- **Patients requiring therapy should be entered into available clinical trials where possible**
- **Outside a clinical trial, CHOP or FC would be considered as standard therapies. (GRADE 1B)**
- **Immunomodulatory therapies such as steroids, ciclosporin, thalidomide and lenalidomide have some evidence of efficacy in chemo-refractory cases. (GRADE 2B)**
- **Consolidation with auto-HSCT should be considered for patients with chemosensitive disease in first remission or after relapse (GRADE 2B)**
- **Routine CNS prophylaxis is not warranted**.

8. Anaplastic Large cell lymphoma- ALCL

- **The International Prognostic Index has predictive value in ALCL but ALK positivity is the most important prognostic factor.**
- **Patients with limited stage anaplastic large cell lymphoma and no adverse prognostic features by IPI should be treated with 3-4 cycles of CHOP chemotherapy and involved field radiotherapy.**
- **All other patients should be entered into a clinical trial or receive 6-8 cycles of CHOP chemotherapy. (GRADE 1A)**
- **ALK-neg ALCL should be treated as for PTCL-NOS**
- **Primary cutaneous ALCL (ALK-neg) should be managed with local excision +/- radiotherapy and chemotherapy reserved for those patients with systemic disease**
- **At relapse patients should receive platinum-based chemotherapy or an alternative salvage regimen such as brentuximab vedotin and patients with chemosensitive disease should be considered for transplant**

9. Extranodal NK/T-cell lymphoma, nasal type

- **Diagnosis and staging uses the same investigations and techniques as for PTCL-NOS (see above). Demonstration of EBV virus in the biopsy is important diagnostically.**
- **Assigning a conventional IPI score is of limited value as most cases are localised and have a low score, yet the survival is still poor (GRADE 1B)**
- **The distinction at diagnosis between localised disease and disseminated disease is important as the latter has a dismal prognosis and might be considered for experimental therapy as first line if available (GRADE 1B)**
- **Assessment of EBV by PCR can be helpful in monitoring disease and may have prognostic relevance**
- **Outcome is unsatisfactory with CHOP-like therapy and entering patients into relevant clinical trials if available is recommended.**
- **Patients with localised disease should receive radiation with 50-55 Gy (GRADE 1B)**
- **The value of additional chemotherapy (CHOP, etoposide-based or asparaginase-based) for local disease remains unclear but is considered conventional pending more information (LEVEL GRADE 1B)**
- **Asparaginase-containing regimens should be considered in disseminated first-line and in relapsed or refractory disease (GRADE 1B)**
- **High dose therapy is unproven and there is no basis to recommend it outside a trial**

10 Enteropathy-Associated T-cell lymphoma (EATL)

- **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 (GRADE 1C)**
- **Assigning a conventional IPI score is of limited value as there is no good prognostic group and most cases are stage I-IIE.**
- **If there are trials available at the time of diagnosis, entry should be strongly considered as there is no satisfactory standard therapy.**
- **CHOP-like therapy, with or without an up-front autograft remains a common approach outside a trial and adoption of a more intensive approach such as the NCRI/SNLG protocol is a reasonable option in fitter patients (GRADE 2B)**
- **Nutrition is a major issue in managing these patients and dietetic/gastroenterology advice is essential at all stages of treatment and follow-up (GRADE 1C)**

11 Hepatosplenic T-cell lymphoma

- **No satisfactory recommendations can be made from the limited evidence base.**
- **Trial or experimental therapy should be considered if available**
- **Allogeneic bone marrow transplantation could be considered but the evidence is purely anecdotal**
- **Conventional chemotherapy approaches as for PTCL-NOS are the default and there are some survivors reported in the literature (GRADE 2C)**

12. Subcutaneous panniculitis-like T-cell lymphoma SPTCL

- **No conclusive recommendations can be made from the limited evidence base. The cases described in the literature are not uniform**
- **This is not a universally aggressive disease and careful initial assessment and observation should be undertaken before committing to treatment (GRADE 2C)**
- **CHOP-like chemotherapy appears to be effective and produces survivors (GRADE 2C)**
- **Relapsed disease may respond to dose intensification in some patients (GRADE 2C)**
- **Local radiotherapy has a place for good prognosis localised symptomatic skin involvement which does not resolve with topical steroids (GRADE 2C)**

Abbreviations

Adult T-cell leukaemia/lymphoma (ATL)
Allogeneic haemopoietic stem cell transplantation (allo-HSCT)
Anaplastic large-cell lymphoma (ALCL)
Anaplastic lymphoma kinase (ALK)
Angioimmunoblastic T-cell lymphoma (AITL)
Ataxia telangiectasia (AT)
Autoimmune haemolytic anaemia (AHA)
Autologous haemopoietic stem cell transplantation (auto-HSCT)
Central nervous system (CNS)
Complete remission (CR)
Computed tomography (CT)
Cutaneous T-cell lymphoma (CTCL)
Diphtheria toxin fusion protein (denileukin difitox)
Direct antiglobulin test (DAT)
Disseminated intravascular coagulation (DIC)
Disease-specific survival (DSS)
Enteropathy-associated T-cell lymphoma (EATL)
Epstein-Barr virus (EBV)
Erythrocyte sedimentation rate (ESR)
Event-free survival (EFS)
Extracorporeal photopheresis (ECP)
Failure-free survival (FFS)
haemopoietic stem cell transplantation (HSCT)
Heat shock protein 90 (HSP90)
Human T-cell leukaemia virus I (HTLV-I)
Immune thrombocytopenia (ITP)
Interferon-α (IFN-α)
International prognostic index (IPI)
International T-cell Lymphoma Project (ITLP)
Involved field radiotherapy (IFRT)
Japan Clinical Oncology group (JCOG)
Lactic dehydrogenase (LDH)
Large granular lymphocyte (LGL)
Mycosis fungoides (MF)
Overall survival (OS)
NK -cell lymphoma (NKTCL)
Nucleophosmin-anaplastic lymphoma kinase (NPM-ALK)
Overall response rate (ORR)
Natural-killer (NK)
Non-Hodgkin lymphoma (NHL)
Partial remission (PR)
Peripheral blood (PB)
Peripheral T-cell lymphoma (PTCL)
Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)
Performance status (PS)
P glycoprotein (PGP)
Pneumocystis jiroveci pneumonia (‘PCP’),

Positron emission tomography (PET)
Polymerase chain reaction (PCR)
Progression-free survival (PFS)
Randomised controlled trial (RCT)
Refractory phases of coeliac disease (RCD)
Scottish and Newcastle Lymphoma group (SNLG)
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)
T-cell receptor (TCR)
T-cell large granulocyte lymphocyte leukaemia (T-LGLL)
Terminal deoxynucleotidase transferase (TDT)
Total skin electron beam therapy (TSEB)
T-prolymphocytic leukaemia (T-PLL)
Transplant-related mortality (TRM)
World Health Organisation (WHO)
Zidovudine (AZT)

Chemotherapy Regimens

AMP (doxorubicin, ranimustine and prednisolone)
ATL-G-SCF (vincristine, vindesine, doxorubicin, mitoxantrone, cyclophosphamide, etoposide, ranimustine and prednisolone
BEAM (carmustine, etoposide, cytarabine, melphalan)
CEOP-B (Epirubicin as for CHOP but with epirubicin instead of doxorubicin + bleomycin)
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)
COPBLAM (cyclophosphamide, vincristine, prednisone, bleomycin, doxorubicin, procarbazine)
CVP (cyclophosphamide, vincristine, prednisone)
EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone)
ESHAP (etoposide, methylprednisolone, cytosine arabinoside, and platinum)
FCD (fludarabine, cyclophosphamide and dexamethasone)
FCM (fludarabine, cyclophosphamide, mitozantrone)
GEM-P (gemcitabine, steroids and cisplatin)
IMVP-16 (ifosfamide, methotrexate, etoposide)
IVE (ifosfamide, etoposide, epirubicin)
OPEC/MPEC (vincristine, etoposide, prednisolone and cyclophosphamide /methotrexate, etoposide, prednisolone and cyclophosphamide)
PEGS (gemcitabine, cisplatin, etoposide and methylprednisolone)
RCM (vindesine, doxorubicin, pirarubicin, cyclophosphamide, etoposide, ranimustine, methotrexate, peplomycin, prednisolone)
VAP (vincristine, asparaginase, prednisone)
VCAP (vincristine, cyclophosphamide, doxorubicin and prednisolone)
VECP (vindesine, etoposide, carboplatin, prednisolone)
VICOP-B (etoposide, idarubicin, cyclophosphamide, vincristine, prednisone, bleomycin

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TABLE 1: Mature T- and NK-Cell Neoplasms: WHO Classification 2008

- **Mature T-cell leukaemias**
  - T-cell prolymphocytic leukaemia (T-PLL)
  - T-cell large granular lymphocytic leukaemia (T-LGL)
  - Chronic lymphoproliferative disorders of NK-cells (provisional)
  - Aggressive NK-cell leukaemia
  - Adult T-cell leukaemia/lymphoma (ATL)

- **Nodal Peripheral T-cell lymphomas (PTCL)**
  - Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)
  - Angioimmunoblastic T-cell lymphoma (AITL)
  - Anaplastic large-cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK) positive
  - Anaplastic large-cell lymphoma (ALCL), ALK negative (provisional)

- **Extranodal PTCL**
  - Extranodal NK-/T-cell lymphoma, nasal type
  - Enteropathy- associated T-cell lymphoma (EATL)
  - Hepatosplenic T-cell lymphoma (HSTL)
  - Subcutaneous panniculitis-like T-cell lymphoma ($\alpha\beta$ only) (SPTCL)

- **Cutaneous T-cell lymphoma**
  - Mycosis fungoides (MF)
  - Sézary syndrome (SS)
  - Primary cutaneous CD30+ T-cell lymphoproliferative disease
    - Primary cutaneous ALCL (C-ALCL)
    - Lymphomatoid papulosis (LYP)
  - Primary cutaneous PTCLs
    - $\gamma\delta$ T-cell lymphoma
    - CD8+ aggressive epidermotropic cytotoxic
    - CD4+ small/medium

TABLE 2: Levels of Evidence (*GRADE*)

STRENGTH OF RECOMMENDATIONS:

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as ‘suggest’.

QUALITY OF EVIDENCE

The quality of evidence is graded as high (A), moderate (B) or low (C).

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g. inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis),or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

TABLE 3: Epidemiology and Outcomes for PTCL from the International T-Cell Lymphoma Project (Vose *et al*, 2008)

Type of PTCL	% of all T-cell lymphomas	5-year failure-free survival	5-year overall survival
PTCL-NOS	25.9%	20%	32%
Angioimmunoblastic	18.5%	18%	32%
NK-T-cell	10.4%	Nasal 29% Extranasal 6%	Nasal 42% Extranasal 9%
ATL	9.6%	12%	14%
ALCL, ALK positive	6.6%	60%	70%
ALCL, ALK negative	5.5%	36%	49%
Enteropathy-associated	4.7%	4%	20%
Primary cutaneous ALCL	1.7%	55%	90%
Hepatosplenic	1.4%	0%	7%
Subcutaneous panniculitis-like	0.9%	24%	64%

PTCL- peripheral T cell lymphoma, NOS- not otherwise specified, NK- natural killer, ATL- adult T cell leukemia/lymphoma, ALCL- anaplastic large cell lymphoma, ALK- anaplastic lymphoma kinase

TABLE 4: Biologic Prognostic Markers in PTCL

Reference	Prognostic marker	Outcome
Gascoyne, 1999	ALK positive	Good
Ishida, 2004	CXCR3	Good
Nelson, 2008	del(5q), del(10q), del(12q)	Good
Martinez-Delgado, 2005	NFkB gene signature	Good
Vose, 2008	EBV	Poor
Went, 2006	Ki-67 >80%	Poor
Vose, 2008	% transformed cells >70%	Poor
Asano, 2005	Cytotoxic granules (TIA-1, granzyme B)	Poor
Ishida, 2004	CCR4	Poor
Cuadros, 2007	Proliferation gene signature	Poor

ITLP= International Lymphoma Project; ALK- anaplastic lymphoma kinase; EBV - Epstein Barr virus

TABLE 5: Novel Therapies in PTCL

Study	Agent	Target or drug type	Patient numbers	Disease status	ORR (%)
Merceica, 1994	Pentostatin	Nucleoside analogue	145	Relapsed/refractory	34% , (45% in T-PLL)
Zinzani 2010, Sallah, 2001	Gemcitabine	Nucleoside analogue	39 10	Relapsed/refractory	52% (9 CR) 60%
Spencer 2007, Emmanouilides 2004, Arkenau 2007	Gemcitabine combinations	Nucleoside analogue	30+	Relapsed/refractory	40-70%
Kim, 2006	CHOEP + Gemcitabine	Nucleoside analogue	26	First line	77% (58% CR)
Damaj, 2013	Bendamustine	Alkylator	47	Relapsed/refractory	52% (29%CR)
Enblad 2004	Alemtuzumab	CD52	14	Relapsed/refractory	36 % (21% CR)
Gallamini 2007, Kluin-Nelemans, 2008	Alemtuzumab +CHOP	CD52		First line	90%
Weidmann, 2010	Alemtuzumab + FCD	CD52	38	Relapsed (11); First line (27)	61% (39%CR)
Forero-Torres, 2009	Anti-CD30, iratumumab	CD30	41	Relapsed/refractory ALCL	17%
Pro, 2012	Brentuximab vedotin	CD30 (immuno-conjugate)	58	Relapsed /refractory ALCL	86% (57% CR)
D'Amore 2010	Anti-CD4, zanolimumab	CD4	21	Relapsed/refractory	24% (2CR)
Dang, 2007	Denileukin difitox	Interleukin-2 (IL-2) receptor	27	Relapsed/refractory	48% (22% CR)
Foss, 2013	Denileukin difitox + CHOP	IL-2 receptor	15	Relapsed/refractory	87% (60%CR)
Piekarz, 2011 Coiffier, 2012	Romidepsin	Histone deacetylation	45 130	Relapsed/refractory	38% (27% CR) 25% (19 CR)
O'Connor, 2011	Praletrexate	Folate analogue	115	Relapsed/refractory	27%
Zinzani, 2011	Lenalidomide	Immune modulation	10	Relapsed/refractory	30% (0 CR)

Zinzani, 2007	Bortezemib	Proteasome inhibition NFkB	15	Relapsed/refractory	67% (2 CRs)
Friedberg, 2011	Alisertib	Aurora kinase A inhibitor	8	Relapsed/refractory	57%

NB. This is not an exhaustive list of all new therapies

TABLE 6: Prospective Studies on first-line high-dose therapy and autotransplantation (auto-HSCT) in PTCL

Author (Year)	n	Regimen	Response	% transplanted	End-Points	Comment
Corradini (2006)	62	Mito/Mel or BEAM	66% CR 18% PR	73%	30% (12y EFS) 55% (12y DFS) 34% (12y OS)	2 phase II studies incl. ALK+ ALCL
D'Amore (2012)	160	CHOEP-16 x 4+ BEAM	71% CR/PR	73%	44% 5y PFS 51% (5y OS)	No ALK+ ALCL
Rodriguez (2007b)	26	Mega CHOP +/- BEAM	65 %CR 4?% PR	73%	53% (3y PFS) 86% (3y OS)	No ALK+ ALCL
Mercadal (2008)	41	High CHOP/ESHAP	51% CR 7% PR	41%	30% (4y PFS) 39% (4y OS)	No ALK+ ALCL
Reimer (2009)	83	Cy/TBI	58% CR, 8% PR	66%	36% (3y PFS) 48% (3y OS)	No ALK+ ALCL

ALCL- anaplastic large cell lymphoma, ALK- anaplastic lymphoma kinase, TBI- total body irradiation, Cy- cyclophosphamide. See glossary for drug regimens