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

British Committee for Standards in Haematology

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- **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.**

2. 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**

3. T-PLL

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

4. T-LGL Leukaemia

- **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 LEVEL IIb & GRADE B**
- **Responses may be enhanced by the use of growth factors (erythropoietin and/or GCSF) LEVEL III & GRADE B**
- **Second line treatments include purine analogues, cyclophosphamide and alemtuzumab**
- **Chronic lymphoproliferative disease of NK cells should be managed as for T-LGL**
- **Rare aggressive NK- cell leukaemias occurring in younger adults require a different therapeutic approach (ALL-Type chemotherapy) and consideration of stem cell transplantation (LEVEL IV & GRADE C)**
- **Patients should be entered into clinical trials wherever possible**

5. ATLL

- **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**
    - **AZT + Interferon-α +/- monoclonal antibodies may be considered in the context of a clinical trial LEVEL IIa & GRADE B**
- **Lymphoma - Induction with CHOP or alternative multi-agent regimen plus G-CSF (LEVEL IIa GRADE B)**

  - Concurrent AZT + Interferon-α (LEVEL IIa GRADE B)

  - AZT + Interferon-α maintenance +/- Monoclonal antibodies (MoAbs)

  OR Allogeneic transplant in 1st CR for eligible patients (LEVEL IV & GRADE C)
- **Leukaemia /High grade lymphoma type - Induction with CHOP or alternative multi-agent regimen plus G-CSF (LEVEL IIa GRADE B)**

  - Concurrent AZT + Interferon-α

  - Allo HSCT in 1st CR for eligible patients (LEVEL IV & GRADE C)

  - OR AZT + Interferon-α maintenance +/- MoAbs (LEVEL IV & GRADE C)

  - 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 (LEVEL IV GRADE C)**

6. PTCL-NOS

- **Primary treatment of PTCL-NOS should be within the context of a clinical trial if possible as standard therapy gives disappointing results (LEVEL IIa GRADE B)**
- **Outside trial, CHOP remains the standard therapy. Consideration should be given to consolidation with auto-HSCT (LEVEL IV GRADE C)**
- **Relapsed or refractory disease should be treated with relapse-schedule chemotherapy and considered for Allo-HSCT with reduced intensity conditioning (LEVEL IV & GRADE C) or autologous stem cell transplantation (LEVEL IV & Grade C) or novel therapies within a trial setting**
- **Outside a trial a number of agents show promise, particularly gemcitabine and praletrexate 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 (LEVEL IV GRADE C)**

7. AILT

- **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. LEVEL IIa & GRADE B**
- **Consolidation with auto-HSCT should be considered for chemosensitive disease in first remission or after relapse LEVEL IV GRADE C**
- **Routine CNS prophylaxis is not warranted**.

8. 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 receive 6-8 cycles of CHOP chemotherapy. LEVEL Ib & GRADE A**
- **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 and patients with chemosensitive disease should be considered for transplant**

9. Extranodal NK/T cell

- **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 B recommendation: evidence level III).**
- **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 B recommendation: evidence level IIb).**
- **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 (LEVEL IIa GRADE B).**
- **The value of additional chemotherapy (CHOP, etoposide-based or asparaginase-based) remains unclear but is considered conventional pending more information (LEVEL III GRADE B)**
- **Asparaginase-containing regimens should be considered in relapsed or refractory disease (LEVEL IIb GRADE B).**
- **High dose therapy is unproven and there is no basis to recommend it outside trial.**

10. 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 (LEVEL III GRADE C).**
- **Assigning a conventional IPI score is of limited value as there is no good prognostic group and most cases are stage I-IIE.**
- **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 (LEVEL III GRADE C).**
- **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. The current UK NCRI study for this disease is recommended.**
- **CHOP-like therapy, with or without an up-front autograft remains a common approach outside trial but evidence of efficacy is lacking and adoption of a more intensive approach such as the NCRI/SNLG protocol is a reasonable option in fitter patients (LEVEL IV GRADE C).**
- **Nutrition is a major issue in managing these patients and dietetic/gastroenterology advice is essential at all stages of treatment and follow-up (LEVEL III GRADE B).**

11. Hepotosplenic T cell

- **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 (LEVEL IV GRADE C)**

12. 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 (LEVEL IV GRADE C)**
- **CHOP-like chemotherapy appears to be effective and produces survivors (LEVEL IV GRADE C)**
- **Relapsed disease may respond to dose intensification in some patients (LEVEL IV GRADE C)**
- **Local radiotherapy has a place for good prognosis localised symptomatic skin involvement which does not resolve with topical steroids (LEVEL IV GRADE C)**

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

There is no previous guideline for this topic. These guidelines have been 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 June **2010**
- Consultation with representatives of other specialities including clinical oncology
- Assessment of the level of evidence and grade of recommendation as set out in tables 2A and 2B. Recommendations made were based on the literature review and a consensus of expert opinion.
- Adherence to the BCSH procedure for guidelines development (http://www.bcshguidelines.com/process1.asp)
- Production of a draft guideline by the writing group, this being revised by consensus by members of the Haemato-oncology Task Force of the BCSH.
- Final revision of the guideline by a sounding board of approximately 50 UK haematologists, the BCSH and the British Society of Haematology Committee with comments being incorporated where appropriate

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.

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 (ATLL).
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 most 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. However, in PTCL stage was altered in less than 10% (Horwitz *et al*, 2006) and did not change treatment recommendations. 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). 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

- **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 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).

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, Ki-67, *TP*53 gene abnormalities, 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 ATLL (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. Preliminary 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) and **cytotoxic T-cell** derivation (Iqbal et al, **2010a)** identify different subgroups within PTCL-NOS which are associated with different prognoses. In the future it may be possible to identify new therapeutic targets using these subtype–specific gene signatures (Agostinelli *et al*, 2008).

Recommendations

- **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 5^{th} and 6^{th} 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)

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.

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).

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.

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 pilot study in 11 patients treated with alemtuzumab as first line therapy, 100% achieved a CR and 64% remained alive at a median follow up of 12 months (Dearden *et al,* 2009). However, a recent pilot study (UKCLL05) showed decreased efficacy when the subcutaneous route of administration was used. 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*, 2007). Of 18 patients (12 therapy-naive) treated with induction chemotherapy there were 4 CR and 8 PR giving an ORR to FCM of 66%. 16 patients proceeded to consolidation therapy increasing the overall response rate to 87%. The median OS was 19.2 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). The largest study reports 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 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. Among other reports of allo-HSCT, (Gadaret *et al,* 2001; De Lavallade *et al,* 2006; Collins *et al,* 1998; Tanimoto *et al,* 2005) the outcome appeared to be 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 should therefore be considered.

Recommendations

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

2. T-LGL Leukaemia

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.

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. 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 CD57and 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 following allogeneic SCT, in association with B-cell malignancies and in imatinib-treated patients with chronic myeloid leukaemia. No consistent chromosomal abnormalities have been described in T-LGL.

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).

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.

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.

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.

Recommendations

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

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

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).

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.

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

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.

Recommendations

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

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

Incidence and epidemiology
ATLL 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 ATLL of 1-5%. The development of ATLL 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)

Presentation, diagnosis and staging

ATLL 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 ATLL 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 ATLL 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 ATLL. The acute form is characterised by a rapidly increasing white cell count and hypercalcaemia. In contrast the lymphoma type has < 4.0 x 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 ATLL 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).

ATLL 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 ATLL 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).

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.

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 ATLL should be monitored.

Conventional Chemotherapy

Despite significant advances in understanding the pathogenesis of ATLL, 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 ATLL 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 ATLL. 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 (AZT) and interferon-α (IFN-α) have reported significant activity in patients with ATLL, 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. A recent meta-analysis on 195 patients confirmed that response rate and survival are improved when these drugs are used as first line therapy (Hermine *et al*, 2007). Patients with chronic and smouldering subtypes had 100% survival after 10 years. Lymphoma patients, however, 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. In the future it may be possible to 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) Clinical trials are needed to better define the roles of these agents.

Novel Agents

Several possible new approaches to the treatment of patients with ATLL 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 ATLL 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). The use of unrelated donors has also been shown to be feasible in retrospective analyses by the Japan Marrow Donor Program (Kato *et al,* 2007). Age and remission status at transplant have been identified as significant predictors of survival and since the median age at presentation with ATLL is approximately 60 years, reduced-intensity conditioning is favoured for the majority of patients. The estimated 3-year overall and relapse-free survival, and disease relapse have been reported as 45.3, 33.8 and 39.3%, respectively in a study of 40 patients (Fukushima *et al,* 2005). 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). ATLL 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.

Recommendations

- **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**
    - **AZT + Interferon-α +/- monoclonal antibodies may be considered in the context of a clinical trial LEVEL IIa & GRADE B**
- **Lymphoma - Induction with CHOP or alternative multi-agent regimen plus G-CSF (LEVEL IIa GRADE B)**
  - Concurrent AZT + Interferon-α (LEVEL IIa GRADE B)
  - AZT + Interferon-α maintenance +/- Monoclonal antibodies (MoAbs)
  OR Allogeneic transplant in 1st CR for eligible patients (LEVEL IV & GRADE C)
- **Leukaemia /High grade lymphoma type - Induction with CHOP or alternative multi-agent regimen plus G-CSF (LEVEL IIa GRADE B)**
  - Concurrent AZT + Interferon-α
  - Allo HSCT in 1st CR for eligible patients (LEVEL IV & GRADE C)
  - OR AZT + Interferon-α maintenance +/- MoAbs (LEVEL IV & GRADE C)
  - 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 (LEVEL IV GRADE C)**

II. Nodal PTCL

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

Incidence / 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 but such discussion is beyond the scope of this guideline.

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.

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%

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 (Gressin *et al,* 2006). 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 compared VIP/ABVD vs CHOP and showed no difference in event free survival (EFS) or OS (Gressin *et al,* 2006). The Nordic group demonstrated some improvement with 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). 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 current NCRI trial of CHOP chemotherapy with the addition of the monoclonal antibody alemtuzumab is open in some centres and is a recommendation for initial therapy. 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 a 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 needs to 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. 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.
The ECOG group are also looking at adding novel therapy to CHOP and currently have a Phase III trial comparing CHOP with or without bevazucimab. Gemcitabine combinations are also being explored in the first-line setting e.g. CHOP, etoposide and gemcitabine (Kim JG e*t al,* 2006), and the SWOG group are conducting a Phase II trial of gemcitabine, cisplatin, etoposide and methylprednisolone (PEGS).

A number of more novel agents have been investigated in PTCL but most data, as expected, is in relapsed/refractory disease (Foss, 2010).

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 Nordic group presented similar results in abstract form (d'Amore *et al,* 2006.)

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. 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, particularly when intending to consolidate with a transplant.

There are emerging data of interest for other agents (Table 5). 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*, 2000). 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). 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).
The monoclonal antibody alemtuzumab is of interest. Combinations of this antibody with CHOP are being investigated in forthcoming trials in PTCL NOS as described above and this has followed on from experience in other diseases (notably chronic lymphocytic leukaemia and T-PLL) and promising early clinical data in PTCL (Dearden, 2006; Lundin *et al*, 1998). 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).
Early data on a number of other molecules exists including histone deacetylase inhibitors (depsipeptide) (Piekarz *et al*, 2004), antibodies to CD25 and the IL2–toxin conjugate dinileukin-difitox (Dang *et al,* 2007; Foss *et al,* 2007; Waldmann *et al,* 2007), a novel anti-folate, praletrexate (O'Connor, 2007,2008, 2009), lenalidomide, mTOR inhibitors, anti- CD4 (zanolimumab) (d'Amore *et al,* 2007) and bortezomib (Zinzani *et al ,* 2007). Most promising of these are the histone deacetylase inhibitors (Piekarz *et al,* 2004), bortezomib and pralatrexate, with a response rate of 39% in heavily pre-treated refractory patients (O'Connor *et al,* 2007, 2008, 2009). Praletrexate has recently been approved in the US for treatment of relapsed PTCL and will be reviewed for licensing in the EU this year. *In vitro* praletrexate has been shown to have synergy with gemcitabine and bortezomib and clinical trials evaluating combination therapy are ongoing.The place of these newer agents in therapy is not yet established although, given the poor response in PTCL-NOS to conventional chemotherapeutic agents, they are likely to be critical for progress in the future.

<u>Auto-HSCT for relapsed/refractory PTCL</u>
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.

<u>Allo-HSCT for relapsed/refractory PTCL</u>
Most retrospective studies of allo-HSCT in lymphoma have not analysed results for patients with T-cell disease separately however a small number of reports have been published. 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 stimulated the development of reduced intensity conditioning regimens, which seek to maintain the graft-versus-tumour

effect whilst minimising regimen related problems. So far there are few studies of reduced intensity conditioned (RIC) -allo HSCT in T-cell lymphoma. A pilot study of 17 patients which included 9 PTCL-U, 4 AITL and 4 ALK- ALCL reported a non-relapse mortality at 2 years of only 6% following a conditioning regimen that incorporated thiotepa, fludarabine and cyclophosphamide (Corradini *et al*, 2004). Severe acute or chronic extensive graft versus host disease (GvHD) was reported in 3 patients overall and with a median follow up of 28 months, 12 were in complete remission. Two patients achieved disease control after donor lymphocyte infusion, providing further evidence for a graft versus T-NHL effect. Short follow up of 10 patients who received fludarabine and cyclophosphamide conditioning after an alemtuzumab containing induction regimen showed a similarly encouraging outcome with 6 continuing remissions but chronic extensive GvHD in 5 (Wulf *et al*, 2005). Further prospective trials addressing the role of RIC-allo-HSCT in PTCL NOS 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 tend in more cases to have 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.

Recommendations

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

7. Angio-immunoblastic T cell lymphoma

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). 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.

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 half 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 (50-83%), 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).

A number of autoimmune phenomena have been reported in association with AITL. These include autoimmune haemolytic anaemia (13%) (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).

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). **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)**

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. The current UK trial is examing front-line therapy with fludarabine and cyclophosphamide.

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 antiangiogenic agent in a few patients, either following relapse or in refractory AITL, with promising results (Strupp *et al,* 2002, Dogan *et al*, 2005). 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). Rituximab is being investigated in combination with CHOP chemotherapy, the latter in cases of AITL with a substantial number of $CD20^+$ large B-cells or refractory AIHA or ITP (Joly *et al*, 2004).

Auto-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 ≥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 not been assessed separately but may be considered for young patients with multiple poor prognostic factors in the setting of a clinical trial.

Recommendations

- **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. LEVEL IIa & GRADE B**
- **Consolidation with auto-HSCT should be considered for patients with chemosensitive disease in first remission or after relapse LEVEL IV GRADE C**
- **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)**

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

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.

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).

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). Therefore ALK-pos ALCL should be treated with CHOP-like chemotherapy in adults 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) that 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 antibodies directed at the CD30 antigen (a member of the TNF receptor superfamily) are 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) and antibody–drug conjugates are in phase I trials (Hamblett *et al.,* 2005). Case reports have documented sustained responses to daclizumab (CD25 antibody) in refractory ALCL (Linden 2004; Grigg *et al.,* 2006). Responses have also been observed in ALCL patients included in phase I trials of 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).

8 b. 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. 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. They express CD30 and 85% have a T-cell phenotype, the remainder being null. Prognosis lies between ALK+ ALCL and PTCL-NOS, with 5-year OS of 49% compared to 19% for PTCL-NOS Currently the management is the same as for ALK-pos ALCL but since the outcomes are less good it is recommended that the standard management should become the same as that for PTCL-NOS.

8 c. 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.

Recommendations

- **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 receive 6-8 cycles of CHOP chemotherapy. LEVEL Ib & GRADE A**
- **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 and patients with chemosensitive disease should be considered for transplant**

III. Extranodal PTCL

<u>9. Extranodal NK/T-cell lymphoma, nasal type</u>
Introduction

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'.

Incidence and epidemiology

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.

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. Blood and marrow tend not to be involved (Vose *et al*, 2008; Kim *et al*, 2008) but when they are this may lead to confusion with aggressive NK-cell leukaemia. Certainly, 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 and distant extranodal structures such as skin, testis and gut (Li *et al,* 2009). Other cases present as widespread extranodal disease, with or without nasal involvement and these patients are systemically unwell (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)

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.

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 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,* 2009, Obama et al, 2003). No formal comparisons with CHOP have been made and data with asparaginase in 1st line therapy is needed. 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 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. 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.

Recommendations

- **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 B recommendation: evidence level III).**
- **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 B recommendation: evidence level IIb).**

- **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 (LEVEL IIa GRADE B).**
- **The value of additional chemotherapy (CHOP, etoposide-based or asparaginase-based) remains unclear but is considered conventional pending more information (LEVEL III GRADE B)**
- **Asparaginase-containing regimens should be considered in relapsed or refractory disease (LEVEL IIb GRADE B).**
- **High dose therapy is unproven and there is no basis to recommend it outside a trial**

10. Enteropathy-Associated T-cell lymphoma (EATL)

Introduction

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.

Incidence and epidemiology

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.

Presentation

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.

Diagnosis and staging

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.

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.

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 and participation in this wherever possible is recommended (chief investigator Dr Anne Lennard, Newcastle). 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).

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.

Recommendations

- **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 (LEVEL III GRADE C).**
- **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. The current UK NCRI study for this disease is recommended.**
- **CHOP-like therapy, with or without an up-front autograft remains a common approach outside a trial but evidence of efficacy is lacking and adoption of a more intensive approach such as the NCRI/SNLG**

protocol is a reasonable option in fitter patients (LEVEL IV GRADE C).

- **Nutrition is a major issue in managing these patients and dietetic/gastroenterology advice is essential at all stages of treatment and follow-up (LEVEL III GRADE B).**

11. Hepatosplenic T-cell lymphoma

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).

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.

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.

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.

Recommendations

- **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 (LEVEL IV GRADE C)**

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

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.

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.

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 $\gamma\delta$ subtypes from this diagnostic category and underlines the impact of HPS in the $\alpha\beta$ expressing cases. (Willemze *et al,* 2008).

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 $\alpha\beta$-expressing cases in the recent WHO classification seems highly clinically

relevant and these patients may have a better prognosis than was previously thought.

Recommendations

- **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 (LEVEL IV GRADE C)**
- **CHOP-like chemotherapy appears to be effective and produces survivors (LEVEL IV GRADE C)**
- **Relapsed disease may respond to dose intensification in some patients (LEVEL IV GRADE C)**
- **Local radiotherapy has a place for good prognosis localised symptomatic skin involvement which does not resolve with topical steroids (LEVEL IV GRADE C)**

Abbreviations

Adult T-cell leukaemia/lymphoma (ATLL)
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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Levels of evidence and grades of recommendation

Levels of Evidence (*Quality of evidence*)

Ia	*High (A)*	Evidence obtained from meta-analysis of randomised controlled trials
Ib	*High (A)*	Evidence obtained from at least one randomised controlled trial
IIa	*Moderate (B)*	Evidence obtained from at least one well-designed, non-randomised study, including phase II trials and case-control studies
IIb	*Moderate (B)*	Evidence obtained from at least one other type of well-designed, quasi-experimental study, .i.e. studies without planned intervention, including observational studies
III	*Moderate (B)*	Evidence obtained from well-designed, non-experimental descriptive studies. Evidence obtained from meta-analysis or randomised controlled trials or phase II studies which is published only in abstract form.
IV	*Low (C)*	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of Recommendation

Grade A Evidence level Ia, Ib	Recommendation based on at least one randomised controlled trial of good quality and consistency addressing specific recommendation
Grade B Evidence level IIa, IIb, III	Recommendation based on well conducted studies but no randomised controlled trials on the topic of recommendation.
Grade C Evidence level IV	Recommendation based on evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

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 (ATLL)

- **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: 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%
ATLL	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, ATLL- adult T cell leukemia/lymphoma, ALCL- anaplastic large cell lymphoma, ALK- anaplastic lymphoma kinase

TABLE 3: 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 4: 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)
Sallah, 2001	Gemcitabine	Nucleoside analogue	10	Relapsed/refractory	60%
Spencer 2007, Emmanouilides 2004, Arkenau 2007	Gemcitabine combinations	Nucleoside analogue	31	Relapsed/refractory	40-70%
Kim, 2006	CHOEP + Gemcitabine	Nucleoside analogue	26	First line	77% (58% 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%
D'Amore 2007	Anti-CD4, zanolimumab	CD4	21	Relapsed/refractory	24%
Dang, 2007	Denileukin difitox	Interleukin-2 (IL-2) receptor	27	Relapsed/refractory	48% (22% CR)
Foss, 2008	Denileukin difitox + CHOP	IL-2 receptor	15	Relapsed/refractory	87% (60%CR)
Piekarz, 2004	Depsipeptide	Histone deacetylation	36	Relapsed/refractory	30% (27% CR)
O'Connor, 2008	Praletrexate	Folate analogue	>100	Relapsed/refractory	27%
Zinzani, 2007	Bortezemib	NFkB		Relapsed/refractory	67% (2 CRs)

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

TABLE 5: 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 (2006)	121	CHOEP-16 x 4+ BEAM	71% CR/PR	73%	63% (3y 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)	56/83 (66%)	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