Guidelines for the Management of Mature T-cell and NK-cell Lymphomas (*excluding cutaneous T-cell Lymphoma).* A British Society for Haematology Guideline

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Methodology

This guideline was developed according to the BSH process at http://www.b-s-h.org.uk/guidelines. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria are described at http://www.gradeworkinggroup.org.

Literature review details

Ovid MEDLINE and Pubmed were searched for English language articles up to December 2020 using the keywords: peripheral T-cell lymphoma, T prolymphocytic leukaemia, large granular lymphocyte leukaemia, adult T-cell leukaemia lymphoma, anaplastic large cell lymphoma, peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, extranodal NK/T-cell lymphoma, aggressive NK cell leukaemia, enteropathy associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, hepatosplenic T-cell lymphoma.

Review of the manuscript

Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee, Haematology Oncology Task Force and the members of Haematology Oncology sounding board of BSH. It was also on the members section of the BSH website for comment.

Introduction

The mature or peripheral T-cell neoplasms are a heterogeneous group of rare disorders arising from clonal proliferation of mature post-thymic lymphocytes. Natural killer (NK) cells are part of the innate immune system although they have functional

similarities to T cells; neoplasms arising from NK cells are considered within the same broad disease group. The World Health Organization (WHO) classification of haemopoietic neoplasms categorized these diseases into those with predominantly leukaemic (disseminated), nodal, extra-nodal or cutaneous presentation (Table 1). Further delineation is based on clinical features, morphology, immunophenotype and genetics. The 2016 revision of the WHO classification incorporated scientific advances in cell ontogeny and molecular signatures of certain subtypes(1).

Accurate diagnosis of peripheral T-cell lymphomas (PTCL) is challenging with relatively high discordance rates reported(2). It is essential that PTCL histology is reviewed by haematopathologists with expertise in PTCL diagnostics.

Nodal PTCL are virtually all 18F-fluorodeoxyglucose (FDG) avid on positron emission tomography (PET-CT) scans. Although baseline PET-CT upstages only a small proportion of cases, additional sites of disease are identified in up to 50%(3). End of treatment PET-CT is increasingly used to guide HSCT decisions. Bone marrow involvement in nodal PTCL occurs in up to 35% of patients but studies report a lower sensitivity of PET-CT in identifying marrow disease compared to Hodgkin lymphoma and diffuse large B-cell lymphoma(4, 5).

Most PTCL subtypes are associated with poor clinical outcomes with conventional chemotherapy, and from the outset, consideration should be given to clinical trial and haematopoietic stem cell transplant (HSCT) options. It is recommended that all PTCL cases, newly diagnosed and relapsed/refractory, are discussed at a regional lymphoma MDT to include expert pathology review and discussion of treatment options. In addition, young adults aged under 25 years of age should be discussed with a Teenage and Young Adult (TYA) specialist. Excellent outcomes for ALCL have been reported in paediatric series and these protocols may be preferable over

adult regimens on a case-by-cases basis considering clinical presentation, individual preferences, and late toxicity risk.

1.1. Recommendations – general

- **All PTCL cases, should be discussed at a regional lymphoma MDT to include expert pathology review and clinical management recommendations (GRADE 1B).**
- **All PTCL cases under the age of 25 years should be discussed with a TYA specialist (GRADE 1B).**
- **Re-biopsy at relapse is essential where clinically feasible (GRADE 1B).**
- **A staging and end of treatment PET-CT is recommended for all non-leukaemic PTCL types (GRADE 1C).**
- **A bone marrow biopsy is recommended in nodal PTCL for accurate staging (GRADE 1C).**
- **All PTCL cases, both untreated and relapsed/refractory, should be considered for a clinical trial wherever possible (GRADE 1B).**

2. <u>T-cell Prolymphocytic Leukaemia (T-PLL)</u>

2.1. Incidence and epidemiology

T-PLL is rare and accounts for approximately 2% of all small lymphocytic leukaemias in adults with a median age of 61 years(6).

2.2. Presentation, diagnosis, and staging

T-PLL typically presents with splenomegaly, lymphadenopathy and leucocytosis, frequently >100 x 10^9/l(7). Less commonly, other organs and skin are involved. Up to 30% of patients are asymptomatic at diagnosis(8).

The circulating prolymphocytes have distinctive morphology and express mature T-cell markers including CD7 with variable expression of CD4 and CD8. Conventional cytogenetic analysis usually demonstrates complex abnormalities(9). Over 90% of cases show a rearrangement of *TCL1A/B* and *MTCP1*(10). Abnormalities of chromosome 8 are seen in over half, and the *ATM* gene (11q22.3) is frequently disrupted(11).

2.3. Prognosis

Overall prognosis is poor with a median survival less than 2 years from initiation of treatment.

2.4. First-line treatment

A 'watch and wait' approach is appropriate for asymptomatic T-PLL, although disease progression is invariably seen within 1-2 years. When indicated, the aim of treatment is to achieve a complete response (CR). Early consideration should be given to consolidative allogeneic haemopoeitic stem cell transplantation (allo-HSCT) for potentially eligible patients.

2.4.1. Chemotherapy

T-PLL is relatively resistant to conventional chemotherapy, with short responses to CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisolone), pentostatin and bendamustine reported(12, 13).

2.4.2. Alemtuzumab

Data supporting use of alemtuzumab are derived from single-arm phase 2 studies, with high overall response rate (ORR) (51-91%) and CR (40-81%), particularly in the first-line setting where a 12 month progression-free survival (PFS) rate of 67%, and a median overall survival (OS) of 24 months are reported(14, 15). Intravenous alemtuzumab, at a dose of 30 mg 3 times per week after dose escalation (3, 10, 30

mg) in the first week, appears superior to subcutaneous administration, although no direct comparative data exist(14, 16, 17). There are no data to support the use of alemtuzumab maintenance(17). Opportunistic infection prophylaxis (co-trimoxazole and aciclovir) and monitoring for cytomegalovirus (CMV) re-activation using quantitative polymerase chain reaction (qPCR) testing are essential.

2.5. Relapsed/refractory disease

Treatment options for relapsed/refractory disease are very limited. Clinical trials should be considered if available. Approximately 50% of patients will respond to alemtuzumab retreatment after a previous clinical response if the cells continue to express surface CD52(18, 19). However, response duration is typically short and cumulative toxicity an important consideration. A phase II study using alemtuzumab with pentostatin in 13 T-PLL patients produced an ORR of 69%, median OS 10.2 months and PFS of 7.8 months(20). For patients with poor responses to alemtuzumab, or who have bulky/extranodal disease, the addition of pentostatin to alemtuzumab may be beneficial.

2.6. Haematopoietic stem cell transplant (HSCT)

Available data on autologous (auto) or allo-HSCT for T-PLL are limited. Although auto-HSCT showed improved OS and PFS compared to historical controls, relapse rates were higher than after allo-HSCT(21). Allo-HSCT is associated with encouraging OS and PFS, although only 30-40% of patients achieve durable disease control and transplant-related mortality (TRM) remains high(22-25). Nevertheless, allo-HSCT is a potential option for achieving long-term remission in carefully selected patients. Auto-HSCT may be an option for those where allo-HSCT is not feasible, but the weak evidence base should be recognised.

2.7. Recommendations – T-PLL

- **Offer a "watch and wait" approach for asymptomatic T-PLL (GRADE 1C).**
- **Offer intravenous alemtuzumab as first line therapy for T-PLL (GRADE 1B).**
- **Offer antimicrobial prophylaxis active against *herpes zoster* and *Pneumocystis jirovecii* and regular CMV qPCR monitoring during and following alemtuzumab therapy (GRADE 1B).**
- **Consider the addition of a purine analogue to intravenous alemtuzumab in the setting of non-response, slow response or bulky nodal/extranodal disease (GRADE 2C).**
- **Consider alemtuzumab re-treatment where duration of initial response exceeded 6 months (from the end of therapy) and surface expression of CD52 is retained (GRADE 2B).**
- **Consider allogeneic stem cell transplant in first remission for eligible patients (GRADE 2B).**
- **Consider autologous stem cell transplant in eligible patients where the risks of allo-HSCT are considered too high (GRADE 2C).**

3. T/NK-large granular lymphocytic leukaemia (LGLL)

3.1. Background, incidence, epidemiology

LGL leukaemia is defined as persistent (>6 months) clonal expansion of circulating large granular lymphocytes, usually above 2 x 10^9/l, without a clearly identified cause. Median age at diagnosis is 66 years with no gender or racial predilection(26, 27).

3.2. Presentation, diagnosis, staging

Neutropenia is present in approximately 80% of patients and the main cause of morbidity and mortality(28). Anaemia and thrombocytopenia occur in approximately 40% and 20% of patients respectively. Hepatomegaly and splenomegaly also occur. A strong association exists with rheumatoid arthritis, which is seen in almost a third of patients(29), as well as with other autoimmune conditions(30). T-LGL leukaemia has also been associated with clonal B-cell disorders, plasma cell neoplasms and non-haemopoietic tumours(31-33).

Most cases are of T-cell origin and usually demonstrate a CD8+ T-cell receptor (TCR) αβ cytotoxic phenotype. Rarer phenotypes express CD4 or TCR γδ or have an NK-cell phenotype. Although a bone marrow biopsy is not mandated within the WHO diagnostic criteria, this is usually helpful in confirming the diagnosis(34) and clarifying the mechanism of cytopenias. T-cell clonality should be confirmed, usually by TCR gene rearrangement studies. However, clonal TCR rearrangements can be demonstrated in reactive conditions and results of analysis need to be considered alongside immunophenotypic aberrations and clinical context. Activating mutations in *STAT3* have been identified in 20-50% of patients with LGLL and *STAT5b* mutations have also been seen in a smaller proportion of patients(35, 36).

3.3. Treatment

Up to half of patients may not require therapy at diagnosis with treatment generally reserved for those with symptomatic disease or severe cytopenias(37). The quality of evidence supporting all recommendations is low. Retrospective and single-arm prospective studies have reported efficacy for immunosuppressive (rather than cytotoxic) approaches; low-dose weekly methotrexate (30, 34), low dose daily cyclophosphamide (38), and ciclosporin (with therapeutic drug monitoring)(39) confer response rates of approximately 40-60%. In T-LGL leukaemias associated with pure

red cell aplasia, cyclophosphamide and ciclosporin appear to be active(40, 41) whereas methotrexate may be preferred in cases associated with rheumatoid arthritis and/or neutropenia(29). Importantly, time to response can be slow; treatment should be given for a minimum of 4 months before determining quality of response. A short course of steroids or granulocyte colony stimulating factor (G-CSF) can be considered to support cytopaenias whilst awaiting suppression of the T-LGL clone. Response rates with prednisolone monotherapy are low(30). Methotrexate and ciclosporin can be continued indefinitely but cyclophosphamide is often stopped after 8-12 months because of concerns regarding secondary cancers(38).

Second line treatment with alemtuzumab, purine analogs, splenectomy and rituximab has been described in small patient groups(42-45).

An increase in large granular lymphocytes is frequently seen in various clinical contexts including after allo-HSCT. Whilst these cases may fulfill the laboratory criteria for T-LGLL, including oligo- or monoclonality, such patients do not typically experience cytopenias or constitutional symptoms and thus should not be necessarily labelled with a T-LGL leukaemia diagnosis.

3.4. Recommendation – LGLL

- **Asymptomatic patients do not require treatment and can be managed initially by observation only (GRADE 1B).**
- **Offer immunosuppressive treatment for patients with symptomatic cytopenias e.g. transfusion dependence, severe neutropenia (neutrophils <0.5 x 10^9/l or <1 x 10^9/l with infectious sequelae), or clinically significant thrombocytopenia (GRADE 1B).**

- **Consider low dose weekly methotrexate, oral ciclosporin or cyclophosphamide as first line treatment options for those requiring therapy (GRADE 1B). Specific treatment choice may be influenced by individual factors (e.g. co-existence of rheumatoid arthritis, pure red cell aplasia, other co-morbid conditions, or concomitant medications).**
- **Treatment should be continued for at least 4 months before stopping due to lack of response (GRADE 1B).**
- **Consider a short course of steroids or growth factors initially (erythropoietin, G-CSF) to support cytopenias prior to suppression of the LGL clone (GRADE 2B).**
- **Offer an alternative immunosuppressive agent (methotrexate, cyclophosphamide, ciclosporin) upon failure (or intolerance) to first line therapy (GRADE 1B).**
- **Consider alemtuzumab or purine analogues as potential options following failure/intolerance of oral methotrexate, cyclophosphamide and ciclosporin (GRADE 2C).**

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

4.1. Background, incidence, and epidemiology

ATLL is caused by the retrovirus, human T-cell lymphotropic virus 1 (HTLV-1), which is endemic in many parts of the world. In the UK ATLL is seen predominantly in patients of African-Caribbean or west African descent but with increasing numbers of cases observed from other ethnic groups suggesting that HTLV-1 serology should be undertaken in all cases of PTCL(46). First degree relatives and partners of those

with ATLL should be screened for HTLV-1 infection as they are at increased risk of ATLL and other HTLV-1 related inflammatory disorders(47).

4.2. Presentation, diagnosis, prognosis

ATLL classification remains as per the original Shimoyama classification(48). In the UK >75% cases are lymphoma subtype, with a median age at presentation of 53 years. More recently a distinct primary cutaneous entity, without blood or lymph node involvement, has been recognised(49). The prognosis for acute and lymphoma type ATLL remains unchanged with a median survival of only 8.3 and 10.6 months. The median OS of indolent subtypes (chronic and smouldering) remains 2-4 years, with 50% of patients transforming to an aggressive generally fatal subtype at a median of 18 months follow up and with no plateau in the survival curve(50, 51). Three prognostic indices have been developed (JCOG-PI, ATL-PI, modified ATL-PI) but even in the low-risk groups the prognosis remains poor and no subgroups of patients have been identified who would not benefit from allo-HSCT(52-54).

ATLL cells have a characteristic morphology (“flower cells”), although such cells may be infrequent. The immunophenotype is CD3+, CD4+, CD26-, CCR4+, CD7- expressing a dominant TCRvB(55) . Monoclonal integration of HTLV-1 proviral DNA is found in all cases and is useful in distinguishing ATLL from other PTCL in a HTLV-1 carrier(56), which is essential due to differing transplant strategies. A United Kingdom Accreditation Service (UKAS) accredited proviral load monitoring and clonality assays are available at Imperial College (further information www.htlv.eu).

Patients are immunocompromised, opportunistic infections are common and suitable prophylaxis is required. Routine strongyloides serology and treatment of seropositive cases is recommended at diagnosis.

4.3. Treatment

Recommended treatment options have been recently summarised in an International Consensus Report(46). Since overall survival remains dismal with current therapies, all patients should be considered for allo-HSCT and referred promptly at diagnosis. Better outcomes are associated with early transplant (<100 days from diagnosis) and whilst in complete remission(57). Prophylactic central nervous system (CNS) therapy should be considered for all patients with aggressive ATLL subtypes(46).

4.4. Choice of chemotherapy

Nodal disease (lymphoma or acute subtypes with lymphadenopathy) should be treated with a chemotherapy-based approach. CHOP-like protocols remain standard of care(46). Whilst intensive protocols may increase CR rates, the PFS and OS are not significantly improved(58) and concurrent zidovudine/interferon-α may be less well tolerated.

4.5. Zidovudine (AZT)/interferon-α (IFN-α)

The combination of the anti-retroviral drug AZT with IFN-α has demonstrated significant activity in patients with ATLL and improved clinical outcome, particularly in leukaemic sub-groups(59) but also in aggressive subtypes(60). In the aggressive form of acute ATLL higher initial doses of AZT/IFN-α are used before reducing to maintenance dosing in responding patients(61). Lower dosing is also used in chronic/smouldering ATL or when given concurrently with chemotherapy in the lymphoma subtype. G-CSF support is usually required.

The addition of the integrase inhibitor, raltegravir, to transplant conditioning protocols to reduce *de novo* infection of donor stem cells has been recently incorporated into clinical practice although the evidence supporting this strategy is limited(46). Patients with acute/lymphoma type ineligible for transplant should continue with maintenance AZT/IFN-α indefinitely. Oral etoposide-containing maintenance chemotherapy, such

as PEP-C (prednisolone, etoposide, cyclophosphamide, procarbazine) is an option for those who do not tolerate AZT/IFN-α(46).

4.6. Mogamulizumab

Mogamulizumab, a monoclonal antibody targeting CCR4, has demonstrated activity in relapsed or refractory ATLL. In addition, mogamulizumab is licensed in Japan in combination with chemotherapy in first-line therapy, resulting in improved CR rates (52% v 33%) but no improvement in PFS or OS(62). Recent retrospective data suggest that patients harbouring activating CCR4 mutations are those most likely to respond(63). There is however a significant risk of severe steroid-refractory acute graft-versus-host disease (GVHD) when mogamulizumab is used prior to allo-HSCT and it is contraindicated within 50 days of transplant(57). Mogamulizumab responses display a compartment effect (effective in blood, intermediate in skin, and poor in lymph nodes) and thus therapy is most active in leukaemic disease.

4.7. Recommendations - ATLL

- **Offer HTLV-1 screening for all cases of PTCL (GRADE 1B).**
- **Offer all first-degree relatives and partners of those with ATLL testing and/or referral for HTLV-1 screening (GRADE 1B).**
- **Offer all patients with ATLL antimicrobial prophylaxis for opportunistic infections (GRADE 1B). Treatment for all positive *Strongyloides stercoralis* serology cases is recommended even if asymptomatic (GRADE 1B).**
- **All patients with 'smouldering' (skin/lung lesions, opportunistic infections), primary cutaneous, or chronic ATLL, should be offered AZT/IFN-α treatment (GRADE 1C).**

- **Patients with aggressive leukaemic form of ATLL should be offered high dose AZT/IFN-α and non-responders should be switched to chemotherapy (GRADE 1C). All potentially eligible patients should be offered allo-HSCT to consolidate response (GRADE 1B).**
- **Patients with lymphoma, or bulky acute ATLL, should be offered CHOP-like chemotherapy and consideration should be given to concurrent AZT/IFN-α (GRADE1C). All potentially eligible patients should be offered allo-HSCT to consolidate response (GRADE 1B).**
- **Consider CNS-prophylaxis for all patients with acute or lymphoma-type ATLL (GRADE 1B).**
- **For patients ineligible for allo-HSCT, consider maintenance therapy with AZT/IFN-α. If AZT/IFN-α is poorly tolerated, consider oral low dose etoposide-containing chemotherapy (GRADE 1C).**
- **Consider addition of an integrase inhibitor (e.g. raltegravir) to transplant conditioning protocols to prevent neo-infection of donor stem cells (GRADE 2D).**

5. Anaplastic large cell lymphoma (ALCL)

The latest WHO Classification recognizes four distinct subtypes of ALCL: primary systemic anaplastic lymphoma kinase (ALK) positive and ALK negative disease, primary cutaneous types and breast implant associated. These subtypes have differences in immunophenotype, genetics, and clinical behaviour(1).

5.1. Epidemiology and clinical features

ALCL comprises approximately 3% of all adult NHLs and 10-20% of childhood lymphomas. ALK+ ALCL typically occurs in children and young adults with a median

age of 30 years, whereas ALK− ALCL occurs in older adults (median age, 55 years). For both types, most patients are male and present with advanced stage disease, often with B symptoms. Extranodal, especially cutaneous, involvement frequently occur(64).

5.2. Prognosis

The International Prognostic Index (IPI) is useful in risk stratifying patients with systemic ALCL (sALCL) and age is a strong factor underpinning the prognostic difference between ALK+ and ALK− ALCL(65). Age <40 years and a low β_2-microglobulin (<3 mg/dl) have been identified as favorable prognostic factors(66). Recurrent chromosomal rearrangements involving the *DUSP22-IRF4* locus on 6p25.3 have been reported as identifying a subset of ALK− ALCL with favourable outcomes but numbers are small and not all studies have reached the same conclusion(67-69). Rearrangement of *TP63* occurs in 8% of cases and may be associated with particularly poor outcomes(68, 69).

5.3. Management of Limited-stage ALCL

Most patients with sALCL present with advanced-stage disease and there are few reported studies involving limited stage. Whilst favourable outcomes have been reported with short-course (3-4 cycles) CHOP-based chemotherapy and consolidation radiotherapy(70) there is insufficient evidence to recommend abbreviated chemotherapy over standard full-course treatment.

5.4. Management of Advanced Stage ALCL

Previously, CHOP-like chemotherapy represented the standard of care for advanced stage ALK+ and ALK− ALCL. Post-hoc and registry studies have suggested benefit for the addition of etoposide to CHOP, particularly in ALK+ ALCL(71, 72).

First-line treatment with CHP-BV (cyclophosphamide, doxorubicin, prednisolone and brentuximab vedotin) has recently been shown to significantly improve both PFS and OS compared to CHOP(73) and is now considered standard of care for systemic ALCL.

The role of high-dose chemotherapy (e.g. BEAM (carmustine, cytarabine, etoposide, melphalan) or similar) conditioned auto-HSCT consolidation in first complete remission (CR1) is unclear. The favourable outcomes of low-risk ALK+ ALCL (IPI <2 and/or <40 years of age) suggest auto-HSCT consolidation should not be performed in CR1. The Nordic group prospective phase 2 trial (NLG-T-01) included 31 patients with ALK− ALCL and showed a 5-year PFS of 61% and 5-year OS of 70%(74). In the ECHELON2 study consolidative transplant was permitted, but a censored analysis found no advantage in PFS or OS(73). The number of ALCL patients transplanted (approximately 20%) in these studies was too low to evaluate the role of transplantation in CR1.

5.5. Relapsed or refractory ALCL

In a phase II trial of single agent brentuximab vedotin in 58 patients with relapsed or refractory sALCL the ORR was 86% and CRR 66% of patients with impressive long-term outcomes seen in those achieving a CR(75).

Patients responding to CHP-BV as first-line therapy for sALCL who subsequently experience relapse, remain eligible for re-treatment with brentuximab vedotin monotherapy, with high response rates reported(76). Alternatively, in those who are refractory to or experience only a short response following brentuximab vedotin, multiagent non-cross-resistant chemotherapy is appropriate (further detailed under PTCL-NOS).

The role of transplantation in nodal PTCL, including sALCL, is also reviewed under PTCL-NOS.

5.6. Breast implant associated ALCL (BIA-ALCL)

BIA-ALCL is a rare lymphoma associated with textured breast implants. Early diagnosis is crucial as surgical resection is usually curative. It is recommended that possible BIA-ALCL cases are managed in line with recent UK BIA-ALCL guidelines(77).

5.7. Recommendations – ALCL

- **Offer 6 cycles of CHP + brentuximab vedotin (CHP-BV) as first-line therapy for ALK− and ALK+ ALCL (GRADE 1A).**
- **Consider high-dose chemotherapy conditioned auto-HSCT in first complete remission for ALK− ALCL or ALK+ ALCL with high-risk features (e.g. IPI ≥2 and/or age >40 years) (GRADE 2B).**
- **Consider involved-site radiation therapy (ISRT) as consolidation, following 6 cycles of CHP-BV, for patients with early stage ALCL in first response (GRADE 2B).**
- **Offer brentuximab vedotin as second-line therapy for patients with relapsed/refractory ALCL who have not previously been treated with brentuximab vedotin (GRADE 1B).**
- **Consider retreatment with brentuximab vedotin monotherapy for patients with relapsed ALCL who previously responded to CHP-BV (GRADE 2B).**
- **Consider multiagent non-cross-resistant chemotherapy for patients with relapsed/refractory ALCL previously treated with CHP-BV, particularly for those with a short first response (GRADE 2B).**
- **Consider autologous or allogeneic stem cell transplantation as consolidation for relapsed/refractory ALCL based on response to prior therapy, current remission**

quality, co-morbid conditions, patient preferences and estimated risks of transplant toxicities (GRADE 2B).

6. Peripheral T-cell lymphoma: not otherwise specified (PTCL-NOS) and angioimmunoblastic T-cell lymphoma (AITL)

The 2016 WHO classification update(1) recognises two provisional new entities ('follicular T-cell lymphoma' and 'nodal peripheral T-cell lymphoma with a T follicular helper (TFH) phenotype') with a common cell of origin(78-80) and overlapping mutational signatures(81, 82) with AITL. Whilst assessing Tfh markers in PTCL-NOS cases is now part of routine diagnostic work-up, there are as yet insufficient data to guide treatment decisions specifically for these entities. Accordingly, this guideline will refer to the 2008 categories of PTCL-NOS and AITL only when discussing treatment recommendations. However, it is possible that future clinical trial eligibility and treatment decisions will be based on Tfh derivation.

6.1. Prognosis

Prognosis is poor with 5-year failure-free survival (FFS) and OS of 20% and 30% respectively. The conventional IPI score is predictive of outcome. Several specific risk scores have been validated in PTCL-NOS and AITL that may better identify a sub-group with relatively favourable clinical outcomes(83, 84).

6.2. First-line treatment: induction

CHOP chemotherapy remains standard of care. A randomised phase II study comparing CHOP with GEM-P (gemcitabine, methylprednisolone and cisplatin) failed to show an improved CR rate with GEM-P(85). In AITL specifically, a first-line phase II single arm trial of fludarabine and cyclophosphamide (FC) with thalidomide maintenance failed to demonstrate significant activity(86).

Data to support the addition of etoposide to CHOP (CHOEP) are inconclusive. A retrospective German analysis reported that younger patients with a normal serum lactate dehydrogenase (LDH) treated with CHOEP had a superior 3-year EFS, but no OS advantage was observed(71). The Nordic NLG-T-01 study of 160 patients (58% had either PTCL-NOS or AITL) treated with 6 courses of CHOEP-14 (CHOP-14 if >60 years of age) followed by auto-HSCT in responding patients reported a 5-year PFS of 44% although this is an inherently selected group who also underwent auto-HSCT(74). A large retrospective study from South Korea failed to demonstrate a benefit when etoposide was added to CHOP(87).

Alternative dose-intensive chemotherapy strategies have been investigated as a way of improving results of CHOP. Whilst some studies have reported encouraging outcomes in single centre randomised(88) or non-randomised studies(89), others have not demonstrated improved outcomes(90) and as such dose intensified strategies cannot be currently recommended.

The ECHELON-2 (detailed in the ALCL section) trial included only small cohorts of CD30+ PTCL-NOS and AITL impeding meaningful interpretation(73). CHP-BV is currently not licensed for PTCL-NOS and AITL in Europe.

A large international randomized trial comparing Romidepsin-CHOP against CHOP presented in abstract form reported a failure of the experimental arm to improve PFS(91).

The role of CNS prophylaxis is not well studied. In a recent study of 600 cases of PTCL, the overall incidence of CNS relapse was 1.8% in PTCL-NOS and 0.7% in AITL at 5 years(92). Involvement of >1 extra-nodal site was the only significant factor identified to be associated with increased risk, but the low number of events precludes definitive conclusions.

In frail patients unfit for combination chemotherapy high-dose corticosteroids may be useful to control symptomatic disease and can achieve remissions(93).

6.3. Management of limited-stage PTCL

Stage I and II AITL and PTCL-NOS are rare with a paucity of robust data to inform treatment decisions. Compared to limited stage DLBCL, clinical outcomes are poor with 5-year PFS of 52% recently reported (94).

6.4. First-line treatment: consolidation

The role of high dose therapy with auto-HSCT as consolidation in first remission is controversial and there are no randomised trials reported. Several prospective studies have shown encouraging results, on an intention-to-treat basis, with long-term disease-free survival rates of 30-55%(74, 95-97). However, these studies have variable inclusion criteria, endpoints and follow-up duration making comparisons and conclusions difficult. A systematic review and meta-analysis reported a PFS rate of 33% (95% C.I. 14-56%)(98). Comparative, non-randomised, analyses and retrospective studies have also been attempted(99-101). These data are all hampered by disease/treatment heterogeneity, unbalanced treatment groups, and different statistical approaches yielding conflicting results. In summary, the contribution of auto-HSCT to survival outcomes, beyond that achieved by conventional chemotherapy, remains unclear.

Allo-HSCT has theoretical advantages over auto-HSCT including a graft free of tumour cells and a donor T-cell mediated graft-versus-lymphoma effect. An international trial randomised patients to auto- versus allo-HSCT after chemotherapy induction(102). The study was hampered by 38% of participants not undergoing HSCT, largely due to disease progression. Patients proceeding to HSCT had similar 3-year event-free survival (EFS) and OS. The auto-HSCT group experienced lower

TRM but higher relapse rates with the converse reported for the allo-HSCT group. There are few other reports of allo-HSCT transplantation exclusively in first remission.

6.5. Relapsed disease: remission induction

There are no randomised studies to guide the optimal therapy for patients with relapsed PTCL-NOS or AITL. Dexa-BEAM and GDP (gemcitabine, dexamethasone, cisplastin) chemotherapy demonstrated overall response rates of 69% and 64% with a median PFS of 6.4 months and 5.4 months respectively(103, 104). Bendamustine monotherapy achieved an overall response rate of 50% with median PFS of 3.6 months(105). Thus, no clear recommendation for a specific chemotherapy regimen can be made; decisions should be made on individual patient- and treating centre-related factors.

Various non-chemotherapy options have been studied, usually in patients with multiply relapsed disease. Three single-agent therapies currently are approved in the US (romidepsin, belinostat and pralatrexate) but modest response rates, PFS benefit and lack of comparative trial data have precluded these drugs receiving European or UK approval(106-108). In AITL specifically, low quality data have suggested activity of ciclosporin, thalidomide, lenalidomide and azacitidine(109-112). The lack of prospective trials or even formal retrospective studies at present prevents recommendation of these agents until prospective data are available.

6.6. Relapsed disease: role of stem cell transplantation

The outcomes of patients with relapsed PTCL are very poor with a median PFS and OS of only 3.1 months and 5.5 months respectively in PTCL-NOS/AITL patients relapsing after initial therapy(113).

For younger patients with no or few co-morbidities, stem cell transplantation is usually considered as consolidation when in 2nd remission. The evidence supporting auto-HSCT in this setting is weak, largely comprising retrospective series(114-117). Allo-HSCT has been more extensively reported in the relapse setting but most studies are retrospective and include patients with a variety of histologies(118-121). One of the largest studies described allo-HSCT, largely performed beyond first remission, conferring 3-yr PFS and OS rates of 36% and 47% respectively. An international registry study focused on the outcome of allo-HSCT for relapsed AITL specifically(122). Only 45 patients were included, but the 3-year PFS and OS rates were 53% and 64% respectively. Outcomes appeared better with chemosensitive disease prior to transplantation. To conclude, allogeneic transplant is a valid option for suitable patients with chemosensitive relapsed PTCL-NOS and AITL.

Recommendations – PTCL-NOS/AITL

- **Offer CHOP chemotherapy as first-line remission induction therapy (GRADE 1B).**
- **Consider involved-site radiation therapy (ISRT) as consolidation, for responding patients after full-course CHOP, for patients with early stage PTCL-NOS/AITL (GRADE 2A).**
- **Consider high-dose chemotherapy conditioned (e.g. BEAM or similar) autologous stem cell transplantation to consolidate first complete remission (GRADE 2B).**
- **Offer non-cross resistant multiagent chemotherapy as second-line therapy for relapsed/refractory disease (GRADE 1C).**

- **Consider consolidation with an allogeneic stem cell transplant in second or subsequent response (GRADE 2C).**
- **Consider CNS prophylaxis according to the same risk assessment applied for diffuse large B cell lymphoma (GRADE 2C).**

7. Extranodal NK/T-cell lymphoma (ENKTL)

7.1. Background, incidence and epidemiology

This is an aggressive, largely extra-nodal lymphoma, usually of NK-cell type (CD2+, CD56+, CD3ε+), with recognised cytotoxic CD8+ T-cell variants. These very rare tumours are commoner in East Asia and South America, where they may represent up to 28% of all PTCL. They present at median age of 50-60 years and have a male preponderance. Epstein−Barr virus (EBV) is implicated in all cases regardless of ethnicity.

7.2. Presentation, diagnosis and staging

The condition almost invariably presents in extra-nodal sites, classically in the nasal structures with or without disease elsewhere. Extra-nasal disease in the absence of overt primary nasal involvement is recognised.

Accurate staging is critical, given the therapeutic implications. MRI imaging is valuable in establishing extent and informing radiotherapy field for localised disease. PET/CT scanning is useful in detecting occult extra-nodal disease sites. Nasal endoscopy with biopsies may demonstrate clinically inapparent nasal involvement.

EBV should be routinely demonstrated in the biopsy material. Latent membrane protein 1 (LMP1) immunostaining lacks sensitivity for EBV detection whereas Epstein–Barr virus-encoded small RNAs *in-situ* hybridization (EBER-ISH) is highly

sensitive and the established gold standard. Peripheral blood EBV DNA should be quantitated and has value as a response biomarker(123).

CNS involvement is relatively uncommon (5-10%) and insufficient data are available to support routine examination of the CNS or prophylactic therapy. An ENKTL-specific CNS risk model has recently been proposed(124).

7.3. Prognosis

The major determinant of long-term clinical outcome is the presence of extra-nasal involvement. A recent analysis reported a median PFS of 72 months vs 10 months and 5-year OS of 56% vs 34% for nasal and extra-nasal cases respectively(125). A novel prognostic index (PINK) delineated three patient groups with 3-year overall survival of 81%, 62%, and 25% respectively(123).

7.4. Treatment of localised ENKTL

Inherent chemoresistance is common, with poor efficacy of CHOP/CHOP-like schedules(126, 127). Involved field radiotherapy (IFRT) typically given at doses of ≥50 Gy is a central component of first-line therapy(128).

Combined chemoradiation protocols, comprising non-anthracycline platinum-based chemotherapy, with/without asparaginase, are an effective strategy. Radiation is typically delivered concurrently with, ‘sandwiched’ between cycles, or immediately following chemotherapy. A prospective phase II trial of 66 patients using a “sandwich protocol” comprising 2 cycles of LVDP (L-asparaginase, etoposide, cisplatin, dexamethasone), 56 Gy radiotherapy, followed by a further 2-4 cycles of chemotherapy reported a 3-year OS of 70%(129). GELOX (gemcitabine, oxaliplatin, L-asparaginase) followed by radiotherapy resulted in a 5-year survival of 86%(130). A concurrent chemoradiotherapy approach using the DeVIC regimen (carboplatin, etoposide, ifosfamide, dexamethasone) achieved a 5-year OS of 61%(131, 132).

The optimal timing of radiotherapy remains unclear but early delivery in the first weeks after initial chemotherapy appears key for localised ENKTL (133).

7.5. Treatment of advanced stage ENKTL

Anthracycline-based chemotherapy is considered inadequate for the treatment of ENKTL(125). A recent prospective trial of the SMILE regimen (dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) demonstrated an ORR of approximately 80%(134, 135) and 5-year OS of 50% although a third of patients received consolidative auto- or allo-HSCT. Toxicities with SMILE can be significant and a treatment-related mortality of 6-7% has been reported. A randomised study, presented in abstract form, of 42 patients comparing DDGP (dexamethasone, cisplatin, gemcitabine, pegylated asparaginase) with SMILE showed a significantly improved PFS and OS in favour of DDGP(136). Although a relatively small study, DDGP appeared to be well tolerated. DDGP does not contain blood-brain barrier penetrating agents and thus may be less attractive in patients judged to have a high CNS relapse risk. AspMetDex (L-asparaginase, methotrexate, dexamethasone)(137) may be useful for older or less fit patients.

HSCT should be considered as first-line consolidation for newly diagnosed advanced-stage ENKTL but there is no international consensus as to whether auto- or allo-HSCT is preferred. A European retrospective study of 28 patients treated with auto-HSCT reported 2-year PFS and OS of 33% and 40% respectively(138). However, the median number of prior treatment lines was two and only 21% had received L-asparaginase-containing chemotherapy. Similarly, Yhim *et al*. reported 3-year PFS and OS rates of 40% and 52% respectively in advanced stage patients predominantly treated with SMILE(139). Regarding allo-HSCT, a small series reported an encouraging 5-year OS of 57%(140) whilst a larger retrospective

analysis found a 3-year OS of only 28%(141). Differences in prior chemotherapy and patient ethnicity varied significantly between the two studies but a consistent finding was that relapses beyond 2 years were uncommon.

Clinical trials should always be considered, particularly for high-risk and relapsed/refractory ENKTL patients. The anti-CD38 monoclonal antibody daratumumab(142), checkpoint inhibitors with anti-PD1/PD-L1 monoclonal antibodies(143) and EBV-specific T lymphocytes(144) are examples of ongoing novel treatment strategies under investigation for ENKTL.

7.6. Aggressive NK-cell leukaemia (ANKL)

This is a very rare form of leukaemia more prevalent in Asian countries but has been reported in patients of Hispanic and Caucasian origin. Median age at presentation is 40 years. Patients present with fever and marked constitutional symptoms. Disseminated intravascular coagulation, haemophagocytic syndrome, liver dysfunction and multi-organ failure may occur. Hepatosplenomegaly is common whilst lymphadenopathy is usually small volume.

Median overall survival is typically very poor. The largest case series examining outcomes of patients with ANKL suggested that L-asparaginase-containing chemotherapy regimens were more active than chemotherapy alone. Notably, the median survival of those patients who received allo-HSCT was 266 days compared to 36 days for those who did not(145, 146).

7.7. Recommendations – ENKTL and ANKL

- **Offer staging with PET-CT given the different treatment protocols for localised and advanced stage disease (GRADE 1B).**
- **Consider MRI for localised disease to assess local extent (GRADE 2C).**

- **Confirm EBV in the tumour cells using EBER ISH (GRADE 1A).**
- **Consider monitoring EBV DNA copy number in peripheral blood by quantitative PCR, at baseline and during therapy, as a corroborative biomarker of response (GRADE 2B).**
- **Offer non-anthracycline, platinum- and/or L-asparaginase-containing chemotherapy with concurrent or sequential radiation (>50 Gy) for stage I and II disease (GRADE 1B).**
- **Offer a multi-agent, L-asparaginase-containing, non-anthracycline-based regimen, such as DDGP, SMILE or AspMetDex, for stage III and IV disease (1B).**
- **Consider auto- or allo-HSCT to consolidate first response in advanced stage disease; the quality of response to first-line therapy, co-morbid conditions, patient preferences and estimated risks of transplant toxicities should be carefully considered (2B).**
- **For patients with aggressive NK leukaemia, offer an intensive remission induction chemotherapy regimen, akin to that for ENKTL advanced stage disease, with intent to consolidate first response with allo-HSCT (1B).**

8. Aggressive intestinal T-cell lymphoma

8.1. Background, incidence and epidemiology

Previously, enteropathy associated T-cell lymphoma (EATL) was classified as either EATL type I or II based on differences in cellular composition and immunophenotype. The 2016 updated WHO classification sought to more clearly distinguish the two as distinct biological entities.

EATL type I is now simply termed EATL. It is strongly associated with HLA DQ 2 or 8 (95%) and coeliac disease, either overt or silent. EATL typically occurs in patients

with treatment-refractory coeliac disease (RCD) although it may be the presenting feature in adults with previously undiagnosed CD. The complex relationship between overt EATL and the various stages of coeliac disease is reviewed elsewhere(147). EATL type 2 is now designated monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), is not associated with coeliac disease, and is more common in Asian and Hispanic populations.

8.2. Presentation, diagnosis, and staging

Both EATL and MEITL typically present with diarrhoea, abdominal pain, and weight loss with a median age of 62 years and a male preponderance. Up to 50% of cases present with an acute bowel perforation. EATL and MEITL usually involve the jejunum or ileum often with multiple, ulcerative lesions.

Staging should include whole body CT. Data supporting the routine use of staging PET-CT is scarce but may better identify EATL in RCD cases(148) and has greater sensitivity for extra-nodal sites of disease. Co-management with an experienced gastroenterologist and nutritionist is essential in both diagnosis and management.

In EATL, malignant cells usually express αβ TCR and are typically CD4− CD8−, CD56−, CD30+. MEITL, by contrast, is typically positive for γδ TCR, CD8 and CD56.

Indolent intestinal lymphoproliferative disorders can be T- or NK-cell in origin and are usually distinguishable by a protracted clinical history and histological features.

Clinical outcomes are poor, likely due to both adverse disease biology and the frequently observed poor performance status of patients together with malabsorption and malnutrition. Both EATL and MEITL have similar outcomes with median OS of approximately 7 months. Only 10-20% achieved long term disease control in historical cohorts.

8.3. Treatment

There is a paucity of data to inform treatment recommendations. Clinical trials should be strongly considered. Conventional CHOP-based chemotherapy yields response in 50% or more but long-term survival is rare. An intensive protocol (often referred to as the 'Newcastle regimen' or NCRI/SNLG protocol) involving 1 cycle of CHOP followed by IVE (ifosfamide, etoposide, epirubicin) for 3 cycles alternating with intermediate-dose intravenous methotrexate and consolidative auto-HSCT demonstrated favourable outcomes, compared to historical controls treated with CHOP-like chemotherapy alone(149). A follow-on prospective phase II study reported 1-year OS of 45% in 11 EATL/MEITL patients with no late relapses(150). The NLG-T-01 study assessed the benefits of biweekly CHOEP with upfront autologous stem cell transplant and included 21 EATL patients. 5-year OS and PFS were 48% and 38% respectively for the EATL subgroup(74).

A retrospective review of 44 patients with EATL undergoing auto-HSCT showed a relapse rate of 39%, PFS of 54% and OS of 59% at 4 years(151). However only 9% received the Newcastle protocol and >50% of the cohort received CHOP-like induction. Better outcomes were seen if patients were transplanted in first remission.

8.4. Recommendations – EATL/MEITL

- **Offer initial therapy with CHOP, particularly for patients with impaired performance status and/or nutritional deficits (GRADE 1B).**
- **Consider intensification of first-line chemotherapy with non-cross resistant regimens (such as the NCRI/SNLG protocol) followed by consolidation with high-dose chemotherapy conditioned (e.g. BEAM or similar) ASCT for eligible patients (GRADE 2B).**

9. Hepatosplenic T-cell lymphoma

9.1. Background, Incidence and epidemiology

This is a rare entity, mainly affecting 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(152).

9.2. Presentation, Diagnosis and staging

This is a systemic, extra-nodal disease involving the liver, spleen and bone marrow(152-156). The median age at diagnosis is 34 years. The clinical features are accompanied by typical histology showing sinusoidal infiltration with tumour cells. Most cases show a characteristic phenotype, expression of the γδ TCR, and have an isochromosome 7q abnormality(155). A variant expressing the αβ TCR is described(154). The aggressive clinical presentation usually avoids confusion with γδ T-cell LGLL. PET-CT scanning is recommended and typically confirms the absence of lymphadenopathy. In addition to 7q abnormalities, trisomy 8 is frequently seen. Like other γδ PTCLs, *SETD2* and *STAT5B* are recurrently mutated(157).

9.3. Prognosis and treatment

Historically the outlook was very poor, with only occasional survivors reported in the few, small series published(152-154). However, patients included in more recent reports demonstrate the curative potential of allo-HSCT for patients with chemosensitive disease with no relapses observed >1.5-years post-allo-HSCT(158, 159). Small case series suggest that ifosphamide/cytarabine/platinum-containing regimens (e.g. IVAC/ICE) are effective bridging regimens to HSCT. A retrospective review of 25 patients included 18 treated with allo-HSCT reported a 3-year PFS of 48% with only a single case of HSTL relapse suggesting long term survival is

possible(160). The majority of patients who underwent auto-HSCT experienced disease relapse.

9.4. Recommendations – HSTL

- **Offer intensive multi-agent non-anthracycline based chemotherapy regimens (e.g. IVAC or ICE) to all potentially eligible patients (GRADE 2C).**
- **Refer all potentially eligible patients to an allo-HSCT centre early following diagnosis with a plan to offer consolidation allo-HSCT if a suitable donor can be identified (GRADE 1C).**

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Review Process

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the

relevant Task Force and the literature search will be re-run every three years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf).

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