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# Pan-London Haemato-Oncology Clinical Guidelines

Lymphoid Malignancies  
Part 5: Less Common Lymphoid  
Malignancies

January 2020

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## Disclaimer

These guidelines should be read in conjunction with the latest NICE guidance, and all applicable national/international guidance. The prescribing information in these guidelines is for health professionals only. It is not intended to replace consultation with the Haematology Consultant at the patient's specialist centre. For information on cautions, contra-indications and side effects, refer to the up-to-date prescribing information. While great care has been taken to see that the information in these guidelines is accurate, the user is advised to check the doses and regimens carefully and if there is any uncertainty about the guidance provided, you should discuss your queries with a Haematology Consultant or Senior Pharmacist. No set of guidelines can cover all variations required for specific patient circumstances. It is the responsibility of the healthcare practitioners using them to adapt them for safe use within their institutions and for the individual needs of patients.

## Contact us

The writing cycle for the guidelines will be from May-July each year. If you wish to be part of the writing group, please contact us through the following link: [Pan London Blood Cancer](#) (or via [uclh.panlondonbloodcancer@nhs.net](mailto:uclh.panlondonbloodcancer@nhs.net)).

If you wish to report errors or omissions that require urgent attention please contact us via the same email addresses.

# 1 Introduction

This part of the Pan-London Haemato-Oncology Clinical Guidelines focuses on the less common tumours that fall under the umbrella of non-Hodgkin lymphoma (NHL).

There are many different types of NHL. Lymphomas are often described as B-cell lymphomas or T-cell lymphomas, according to whether they began in B-cell lymphocytes or T-cell lymphocytes.

## 1.1 Type of B-cell lymphomas

B-cell lymphomas are more common than T-cell lymphomas. About 9 out of 10 people diagnosed with NHL have a B-cell lymphoma.

The most common types of B-cell lymphoma are:

- diffuse large B-cell lymphoma (DLBCL)
- follicular lymphoma (FL).

(Separate guidelines exist for these most common B-cell lymphomas.)

Other less common types include:

- marginal zone lymphomas
- hairy cell leukaemia
- mantle cell lymphoma
- Burkitt lymphoma
- lymphoplasmacytic lymphoma (also called Waldenström's macroglobulinaemia (WM)).

## 1.2 Types of T-cell lymphomas/leukaemias

### 1.2.1 Peripheral T-cell lymphomas

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of rare malignancies accounting for approximately 10–12% of all lymphoid neoplasms. Most have an aggressive clinical behaviour and, apart from ALK-positive anaplastic large cell lymphoma (ALCL), a poor response to conventional chemotherapy with only 30% survival at 3 years. Patients often present with disease at extranodal sites and poor PS.

*(a) Nodal*

- Peripheral T-cell lymphoma, unspecified
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma (ALK+, ALK-, primary cutaneous)
- Adult T-cell lymphoma/leukaemia.

*(b) Extranodal*

- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma.

*(c) Cutaneous*

- Mycosis fungoides/Sézary syndrome
- Lymphomatoid papulosis.

*(d) T-cell leukaemias*

- T-cell prolymphocytic leukaemia (T-PLL)
- T-cell large granular lymphocyte leukaemia and chronic NK LPD.

## 2 Overview and Generic Guidance

For simplicity, and to avoid repetition in each tumour-specific guideline, general information which is applicable to all rare lymphoid malignancies is covered in this section. It includes generic areas of guidance such as service and multidisciplinary team (MDT) configuration across London, the management of children, teenagers and young adults with lymphomas, patient support and information, management of disease and treatment-related complications, supportive care, treatment summary and care plan, survivorship and rehabilitation, research and clinical trials and end of life care. Specific chapters will then provide tumour-specific information for the individual lymphomas.

## 3 Service Configuration

All new diagnoses and cases under consideration for treatment should be reviewed and discussed in the local multidisciplinary team (MDT) meeting.

It is recommended that cases requiring second line treatment or greater are similarly discussed in the MDT, particularly in view of the wide range of potential management options in this context.

The MDT referral form should include full patient identifier details including NHS number, relevant presenting history, associated symptoms including presence or absence of B symptoms, and co-morbidities.

The recorded MDT outcome should include histological confirmation of diagnosis including grade (1/2, 3a or 3b as per WHO classification), stage and the relevant ICD code with recording of prognostic index/score where applicable. A designated key worker and the agreed management approach, expectant or treatment with specific modality and regimen indicated, should conclude the MDT outcome.

The completed MDT outcome form should be authorised by the MDT lead and distributed to the patient's GP within 24 hours.

### 3.1 Children, teenagers and young adults

Children below the age of 16 years with a diagnosis of lymphoma must be referred to the paediatric oncology team at the principal treatment centre (PTC) and must not be managed exclusively by adult site-specific teams.

- The joint PTC for children aged below 16 years for South Thames is The Royal Marsden (Sutton)/St George's Hospital.
- The PTC for North Thames (including North West London) is Great Ormond Street Hospital/University College London Hospitals.

All patients <1 year from both North and South Thames should be referred to Great Ormond Street Hospital.

Teenagers aged 16–18 should be managed at a PTC for teenage and young adult (TYA) cancers. Young adults aged 19–24 should be given the choice of being managed at a PTC or TYC designated hospital.

- The PTC for TYA for South Thames is The Royal Marsden (Sutton) with TYA designated centres at St George's Hospital, Guy's and St Thomas's Hospital and King's College Hospital.
- The PTC for North Thames (including North West London) is University College London Hospitals, with TYA designated centres at Chelsea and Westminster Hospital (HIV+ skin only), Charing Cross Hospital, and Mount Vernon Cancer Centre.

All patients within this age range, regardless of place of care, should be referred to the TYA MDT at the relevant PTC.

## 4 Patient Information and Support

If the diagnosis is confirmed, patients should be informed that they have a cancer of the blood, bone marrow and immune system. Their prognosis should be discussed including reference to co-morbidities that may influence management approach and prognostic indices as appropriate. It is particularly important that this process is done sensitively, in a timely manner and with consideration of any specific needs and feelings of the patient. Possible management options, including appropriate treatment options, clinical trials and research studies, should be discussed.

All patients must have access to a key worker. This is usually (but not always) the clinical nurse specialist.

The key worker/clinical nurse specialist should ensure that all patients are offered a Holistic Needs Assessment (HNA) at key pathway points, including within 31 days of diagnosis; at the end of each treatment regime; and whenever a person requests one. Following each HNA, every patient should be offered a written care plan. This plan should be developed with the patient and communicated to all appropriate healthcare and allied healthcare professionals.

Written and verbal information is essential, and the key worker/clinical nurse specialist plays a key role in ensuring that patients have access to appropriate and relevant written information about their condition.

The Bloodwise or Macmillan Cancer Support information booklets are good sources of patient information at diagnosis. Patient leaflets are available for all treatment options and are available for download on the following websites:

[www.macmillan.org.uk/information-and-support/lymphoma/lymphoma-non-hodgkin/understanding-cancer](http://www.macmillan.org.uk/information-and-support/lymphoma/lymphoma-non-hodgkin/understanding-cancer)

<https://bloodwise.org.uk/>

Particularly important aspects of communication and patient information may include:

- treatment intent – whether the condition is curable/incurable
- the concept of watch and wait
- the range and types of therapy (including novel treatments and SCT)
- clinical trials
- fertility
- treatment toxicity and late effects.



## 5 Management of Common Disease and Treatment-related Complications

### 5.1 Superior vena cava obstruction

Superior vena cava obstruction (SVCO) is nearly always associated with malignancy, usually lung cancer (80% of cases) but sometimes lymphoma, breast cancer or germ cell tumours. It occurs most commonly in patients with known cancer but can be the presenting feature of a new diagnosis.

#### 5.1.1 Signs

Although the signs of SVCO are characteristic, they are often absent and so an index of suspicion is needed based on tumour type and symptoms:

- thoracic vein distension (65%)
- neck vein distension (55%)
- tachypnoea
- facial/conjunctival oedema (55%)
- central/peripheral cyanosis (15%)
- arm oedema (10%)
- plethora (15%)
- vocal cord paresis (3%).

### 5.2 Cord compression

Spinal cord compression due to malignant infiltration or vertebral collapse requires **immediate** management and referral. Acute oncology clinical guidelines contain detailed information regarding management and referral for spinal cord compression.

### 5.3 CNS involvement

If the patient presents with neurological symptoms or signs, then a lumbar puncture and MRI brain/spine looking for meningeal disease is mandatory.

Treatment of confirmed CNS disease is with methotrexate 12.5mg, cytarabine 50mg and hydrocortisone 50mg. Patients are treated twice weekly (for 4 weeks) until the CSF clears and then once weekly for a further four weeks, then every two weeks until radiotherapy if indicated. Alternatively, intravenous high dose methotrexate and/or cytarabine can be considered as treatment or consolidation.

### 5.4 Febrile neutropenia

Suspected or proven infection in a neutropenic patient is a **medical emergency** and is an indication for immediate assessment and prompt treatment with intravenous (IV) antibiotics **within 1 hour of presentation** to anywhere within the hospital. Patients who are neutropenic following anti-cancer treatment may initially appear well. However, infections may progress within hours to shock or death, especially when due to gram-negative bacilli. If there is clinical suspicion of neutropenic sepsis in existing inpatients, they should be treated within 1 hour of clinical onset, as

defined by baseline observations, Early Warning Score (EWS) or clinical suspicion. Local policy should be followed for antibiotic cover. Patients with neutropenic pyrexia or sepsis should be treated according to local protocols for neutropenic sepsis (and following National Institute for Health and Care Excellence (NICE) guidance).

In addition, for haematology oncology patients the following are mandatory:

- urinalysis
- midstream specimen of urine
- chest X-ray
- swabs: throat (bacterial and viral), CVAD site if present and any other focal lesions as appropriate
- sputum and stool culture
- CMV, EBV, adeno PCR if indicated.

For neutropenic sepsis, use G-CSF to encourage neutrophil recovery; G-CSF can be used prophylactically in those patients with recurrent septicaemia.

## 5.5 Nausea and vomiting

Follow pan-London nausea and vomiting protocol/local policy.

## 5.6 Tumour lysis syndrome (TLS) and hyperuricaemia

See [Annex 1](#) for information on tumour lysis syndrome and [Annex 2](#) for guidance on the use of rasburicase.

Patients with aggressive disease may already be in tumour lysis prior to the initiation of chemotherapy. Tumour lysis is indicated by a high LDH, uric acid, hyperkalaemia, hyperphosphataemia, hypocalcaemia and renal failure. The mainstay of treatment is avoidance by aggressive IV hydration from diagnosis and especially at the start of cytoreductive therapy, rasburicase as per protocol (if G6PD is normal) followed by allopurinol. If TLS does occur, patients undergoing intensive therapy must be supported with appropriate fluid and electrolyte management and, if necessary, ICU transfer with haemofiltration until TLS resolves and renal function improves.

## 6 Supportive Care

Supportive care is very important for all patients with haematological malignancies. There are many aspects to consider and they are carefully documented in current clinical trial protocols. These protocols are available for download and should be consulted for precise details of appropriate supportive care, even if patients are not entering the clinical trial.

Patients should ideally be nursed in isolation rooms with appropriate protocols to prevent infections. Clean, neutropenic diets should be instituted and appropriate infection control measures should be undertaken. Prophylaxis and treatment of infection from presentation should be instituted based on local protocols with antibiotic choice largely dependent on local microbiological flora. For patients who will undergo intensive treatment schedules, a central venous access device should be inserted as soon as is safely possible.

### 6.1 Transfusions

Transfusion triggers should be chosen in advance for patients, depending on co-morbidities. For patients with no co-morbidities or bleeding risk, and in those who do not lead active lifestyles, it would be reasonable to aim for a target Hb > 80g/dL.

Red cell transfusions should be avoided if there is any risk of leukostasis.

Platelets should be transfused when the platelet count is  $<10 \times 10^9/L$ , or  $<20 \times 10^9/L$  in the setting of sepsis.

All platelet products should be single donor collections in order to limit the risk of allo-sensitisation. HLA-typing should be done prior to starting treatment in order to address donor status if transplantation is appropriate for the patient, and in case HLA-matched platelets become necessary during treatment (as often occurs in women who have had children). Irradiated blood products should be requested for patients on protocols containing fludarabine, cladribine and clofarabine and for at least one month prior to a planned SCT.

### 6.2 Haemostasis and thrombosis

Ensure that patients have good control of blood pressure (if they are known to be hypertensive) and do not suffer from constipation – if not appropriately managed, both conditions can increase the risk of severe life-threatening haemorrhage.

Avoid aspirin/non-steroidal anti-inflammatory drugs (NSAIDs) and intramuscular injections (unless platelets  $>50 \times 10^9/L$  if IM L-asparaginase is to be used). Avoid arterial blood gases unless absolutely necessary – ensure platelets  $>50 \times 10^9/L$ .

A proton-pump inhibitor (PPI) should be administered during corticosteroid-containing treatment phases.

### 6.3 Infection prophylaxis

During intensive treatment regimens in induction, intensification and consolidation, patients should receive routine prophylaxis for PCP (co-trimoxazole), HSV/VZV reactivation (acyclovir), bacterial and fungal infections (with either an azole or, during regimens containing vincristine, with non-azole antifungals). For low-risk regimens such as CHOP-21 fluconazole is appropriate. For salvage regimens including high-dose cytarabine an extended triazole such as itraconazole may be

considered (refer to local antifungal guidelines, local protocols on neutropenic sepsis and NICE guidance).

G-CSF is used to hasten recovery of the neutrophil count, decrease risk of infection and reduce hospital stay. However, evidence supporting improved survival with G-CSF is lacking.

A neutropenic diet should be followed until counts recover. Patients should be nursed in a neutral-pressure or positive-pressure isolation room with appropriate air and water filtration systems during inpatient stays and at least during phase 1 induction.

Co-trimoxazole must be stopped one week prior to, and during, high-dose methotrexate intensification. Avoid co-trimoxazole on the day that methotrexate is given when the patient is on maintenance therapy. In the event of allergy to co-trimoxazole, local policies should be followed with an alternative prophylactic agent, such as nebulised pentamidine, oral dapsone or oral atovaquone.

## 6.4 Breathlessness

- Any inpatient showing signs of respiratory distress should be assessed by a physician with knowledge of treatment for patients with lymphoma and, if appropriate, referred for respiratory physiotherapy assessment in accordance with local on-call guidelines, unless of overt metabolic cause.
- Any patient showing signs of non-acute breathlessness should be assessed by a physician with knowledge of treatment for patients with lymphoma. Referral for respiratory physiotherapy assessment and intervention should always be considered.
- Ongoing breathlessness management strategies can be provided by occupational therapy or physiotherapy.

## 6.5 Weight loss

- A screening tool for the assessment of dietary issues should be completed weekly for inpatients and, if issues are identified, a referral should be made to a specialist dietitian.
- Referral for specialist dietetic input should be made in the following instances:
  - Any patient with neutropenia should be provided with information and education on the neutropenic diet and be referred to a specialist dietitian.
  - If artificial feeding is being considered, a referral to the specialist dietitian should be made.
  - Any patient with mucositis should be referred for dietetic assessment, as well as for specialist speech and language assessment.
  - Weight loss/malnutrition should be identified through weekly screening of inpatients.

## 6.6 Pain

People reporting pain should be considered for non-pharmacological intervention including, but not limited to, TENS (transcutaneous electrical nerve stimulation), complementary therapy and psychological intervention such as mindfulness.

## 6.7 Complex symptom management

Discuss with the specialist palliative care team for advice on symptom management, e.g. pain, mucositis, when there is no/poor response to standard interventions. If appropriate, referral can be made to the specialist palliative care team.

## 7 End of Treatment Information

An end of treatment consultation should be offered to every patient. This should include an end of treatment HNA and associated written care plan and should also include the discussion and provision of a comprehensive treatment summary. On successful completion of treatment, both the patient and their GP should be made aware of follow-up plans and potential future disease or treatment-related issues.

### 7.1 Treatment summary and care plan

There are two related but distinct documents which patients should be given at the end of their treatment.

- A **treatment summary** provides a summary of the cancer treatments received by the end of the first treatment, planned follow-ups (including mechanisms for these), and signs and symptoms of which to be aware. Their aim is to provide information not only to the patient but also to the GP about possible consequences of cancer and its treatment, signs of recurrence and other important information. The treatment summary should be completed by the named clinical nurse specialist/key worker with the patient and a copy sent to the GP and the patient.
- A **care plan** is generated as a result of an HNA and is the agreed plan between the patient and healthcare professional about how the identified areas of concern will be addressed. This may cover provision of information, onward referral for specialist assessment and intervention (e.g. breathlessness management), or things which the patient themselves can do (e.g. contact their HR department about graduated return to work options).

#### Recommendation

An end of treatment consultation should be offered to every patient. This should include an end of treatment HNA and associated written care plan and should also include the discussion and provision of a comprehensive treatment summary.

Lymphoma team, key worker and patient support group contact details should be reiterated and details of future follow-up arrangements provided.

Patients should be educated regarding the potential symptoms and signs that might indicate disease progression or recurrence and counselled on the need to re-present to the unit should these occur.

People should be offered access to a health and wellbeing clinic at the end of treatment. This should provide information to enable a person to self-manage any expected consequences of their cancer and its treatment, as well as general health promotion information, including diet and physical activity.

The MDT outcome form and clinic letters will serve to communicate diagnosis, treatment initiation and new lines of treatment with the GP.

## 8 Follow-up Arrangements

All patients need clinical assessment, imaging as dictated by the clinical condition plus additional tests as below. If the patient is in a study, check if any additional tests are necessary and check follow-up interval. Remember that hormonal failure can occur in various systems after both radiotherapy and chemotherapy.

CT scan is routinely performed at 3 months after completion of chemotherapy except for low-grade lymphoma. Discuss with consultant if symptoms of relapse or refer to study protocol. Surveillance imaging is not recommended.

The nature and frequency of follow-up review and investigations for patients will be somewhat tailored by their disease, treatment type, treatment toxicities, disease-related effects, co-morbidities and psycho-social factors.

<b>Standard lymphoma following chemotherapy (adjusted to patient risk)</b>	
3 months	Clinical examination, full blood count and CT
6 months	Clinical examination
9 months	Clinical examination
12 months	Clinical examination (TFTs if neck/mantle radiotherapy)
18 months	Clinical examination
24 months	Clinical examination
Annually until 5 years When discharge can be considered and discussed with consultant (see below)	Clinical examination (TFTs if neck/mantle radiotherapy)
<b>Long-term follow-up – patients with lymphoma in remission for 5 years</b>	
Can be considered for discharge after 5 years with the exception of:	
<ul style="list-style-type: none"> <li>• females treated with mantle radiotherapy, radiotherapy to the neck where the thyroid gland was within the field or radiotherapy to breast tissue who can be discharged at five years but must be referred to the appropriate breast team (as above) for screening and their GP must monitor TFTs yearly (or if symptomatic) commencing 5 years post radiotherapy</li> <li>• males treated with mantle radiotherapy or radiotherapy to the neck where the thyroid gland was within the field may be discharged after 5 years but will require their GP to monitor TFTs yearly (or if symptomatic) commencing at 5 years post radiotherapy</li> <li>• those who had high-dose chemotherapy who remain on surveillance indefinitely unless felt suitable for discharge by the consultant</li> <li>• indolent lymphomas with significant risk of recurrence.</li> </ul>	

All patients should be made aware of the risks of secondary cancers and participate in national cancer screening programmes, and of the increased risk of cardiovascular disease with the need for periodic monitoring of risk factors in general practice.

## 9 Research and Clinical Trials

Where possible, biobanking of all patient blood and tissue samples is encouraged in a certified facility within the context of an ethically approved research framework and in compliance with the Human Tissue Act.

Eligible patients should always be offered the opportunity to consider clinical trials for any stage of disease management. This may be either at the treating centre or in another lymphoma centre.

Occasionally, it may be appropriate to refer patients to centres outside London for clinical trials open elsewhere and, in a reciprocal manner, centres within London may occasionally receive referrals of patients. Such collaboration within and across cancer systems should be supported.

## 10 End-of-life Care

Common causes of death include lymphoma (treatment-resistant disease progression or transformation), therapy-related complications and infections.

Although predicting when death may occur is often inaccurate, it is important to consider and offer discussions with patients, and partners/relatives/carers/friends as appropriate, when it is apparent that disease or its complications are progressing and further treatment is futile.

Such matters require sensitivity and consideration of patients' cultures, beliefs, wishes and communications as well as those of their next of kin, in particular.

Where appropriate, patients should be asked about their preferred place of death, and local and national guidance on resuscitation decisions should be followed.

The best interests of the patient must be at the forefront of discussions and decision-making regarding end-of-life care while early involvement of local palliative care teams (hospital and/or community) will optimally facilitate the formation of individualised end-of-life care packages. Care may be required from specialist palliative care teams.

## 11 Marginal Zone Lymphoma

### 11.1 Introduction

Marginal zone lymphoma (MZL) is an uncommon form of NHL associated with chronic infection and inflammation (e.g. gastric MALT lymphoma and *Helicobacter pylori* infection). Other microbes include *Campylobacter jejuni*, *Borelia burgdoferi*, *Chlamydia psittaci* and hepatitis C. MALT lymphomas of the salivary and thyroid glands are associated with Sjögren's syndrome and Hashimoto's thyroiditis respectively.

Marginal zone lymphoma is usually very indolent, growing slowly.

#### 11.1.1 Classification

Extranodal MZL (MALT)

- gastric (30%)
- non-gastric (70%), e.g. pulmonary, cutaneous, ocular.

Nodal MZL

Splenic MZL

### 11.2 Investigation and diagnosis

#### 11.2.1 General initial assessment

- FBC, differential, DAT
- Renal, liver and bone profile, LDH, Immunoglobulins, paraprotein, B2M
- BM aspirate and trephine with immunohistochemistry
- CT-NCAP (MRI if orbital disease)
- Careful attention to extranodal sites
- Infection screens – hepatitis B and C, HIV, and *H pylori*, chlamydia, etc, as indicated.

#### 11.2.2 Specific investigations – MALT

##### (a) Histology

- Cellular composition includes small lymphocytes, centrocyte-like cells, 'monocytoid' B-cells, plasmacytoid cells
- Invasion of epithelial structures and existing germinal centres
- CD5<sup>-</sup>, CD10<sup>-</sup>, CD19<sup>+</sup>, CD20<sup>+</sup>, CD23<sup>-</sup>, sIgM<sup>+</sup>, sIgD<sup>+</sup> or <sup>-</sup>
- Disease localised to or centred on an extranodal site.

##### (b) OGD

- At diagnostic endoscopy the lesion should be photographed to allow assessment of macroscopic response in follow-up examinations. Multiple biopsies should be taken from the area of abnormality. This is to ensure sufficient diagnostic material is available and to exclude



foci of transformation. Biopsies from normal antral mucosa should be included to assess *Helicobacter* status.

- If histology or CLO test does not identify *Helicobacter*, stool samples for *Helicobacter pylori* antigen should be sent to microbiology.
- The presence of t(11;18) in 25–40% of cases is associated with failure of eradication therapy and disseminated disease but lower risk of high grade transformation.

#### (c) SMZL

- Diagnosis is usually made on **morphology and immunophenotype of PB/BM lymphocytes** in a patient presenting with splenomegaly.
- Often identified in an elderly patient referred with suspected CLL or MCL.
- Low level (<20g/l) serum paraprotein (IgG or IgM) is common.
- Check DAT as AIHA rare but documented.
- Cryoglobulins in HCV+ cases.

### 11.2.3 Poor prognostic features

#### (a) Gastric MALT

- *H pylori* negative
- Tumour invasion beyond the mucosa
- T(11;18)
- Bcl 10 nuclear expression.

#### (b) SMZL

- Hb <120g/dl
- High lymphocyte count (>18 x 10<sup>9</sup>/L)
- Albumin <35 g/l
- LDH >ULN
- TP53 del/mut
- Abnormalities of chromosome 7 (del 7q 22–32)
- High grade transformation (v rare).

## 11.3 Treatment

All patients should be considered for clinical trials where possible.

### 11.3.1 Indications for treatment

- Symptomatic disease
- GI bleeding
- Bulky disease
- Cytopenias.

### 11.3.2 Gastric MALT

#### (a) Primary treatment

Localised stage IE/II E disease should receive *Helicobacter pylori* eradication as primary therapy (remission in 70%).

*Helicobacter pylori* eradication therapy:

- Lansoprazole 30 mg BD – 1 week.
- Amoxicillin 1g BD – 1 week.
- Clarithromycin 500 mg BD – 1 week.
- For alternatives to this regimen dependent on previous attempts at *Helicobacter pylori* eradication or allergies, please see BNF.
- Eradication of *Helicobacter* should be confirmed by stool sample for *Helicobacter* antigen at least 4 weeks after completion of *Helicobacter* therapy.
- **NOTE: patients must stop taking antacids, PPIs, H2 antagonists or bismuth preparations for 2 weeks prior to test.**
- Surgery is generally to be avoided except in emergency situations to control bleeding or repair a perforation; these are very rare in gastric marginal zone lymphoma.
- Follow-up with upper GI endoscopy and biopsy at 6, 12 and 24 months for the first 2 years.

#### (b) Recurrent or resistant gastric MALT

- Patients with recurrent disease after 1 year, stage greater than 1E or persistent disease after *Helicobacter* eradication should be considered for treatment with chemotherapy (rituximab-bendamustine, chlorambucil + rituximab, R-CHOP, R-CVP), single agent rituximab or low-dose IF radiotherapy.
- Patients with persistent/recurrent **asymptomatic** disease after therapy can be followed up by repeat endoscopy without further treatment.
- Patients with persistent/recurrent **symptomatic** disease who have received treatment should be re-discussed in lymphoma MDT for other relevant options.
- For patients with large cell transformation, CHOP and rituximab chemotherapy is recommended.

### 11.3.3 Non-gastric MALT

- Watch and wait in asymptomatic patients
- IF radiotherapy for localised disease
- Rituximab monotherapy
- R+ chemotherapy (as per FL protocols)
- Ocular MALT – consider doxycycline 100 mg BD x 3 weeks.

### 11.3.4 Splenic MZL

- Watch and wait is a reasonable approach in asymptomatic patients (25% may never need treatment).
- Treatment is usually indicated for bulky splenomegaly and cytopenias, and more rarely lymphocytosis.
- Splenectomy (pre-surgical immunisations and post-surgery prophylaxis with penicillin V or clarithromycin) can result in long-term remissions.
- Splenic irradiation may be an alternative in patients not fit for surgery although morbidity is the same.
- Alkylating agents (e.g. chlorambucil) are relatively ineffective.
- Rituximab monotherapy.
- FR, BR or FCR.
- R-CVP is sometimes used but no clear evidence that this is superior to R alone and is less effective than purine analog (PA) +R.
- R-chlorambucil if concerns over frailty.
- R-CHOP for high grade transformation.
- Ribavarin/interferon in HCV+ patients.

### 11.3.5 Nodal MZL

- Watch and wait if asymptomatic
- Stage 1 – consider local RT
- Systemic chemotherapy +R, as per FL protocol.

## 11.4 Supportive care

All patients who have received purine analogues or bendamustine should receive irradiated blood products. See [section 6](#) for general supportive care guidance.

### 11.4.1 Follow-up arrangements

See [section 8](#) for general follow-up arrangements.

#### (a) Gastric MALT

- Eradication of *Helicobacter* should be confirmed by stool sample for *Helicobacter* antigen at least 4 weeks after completion of *Helicobacter* therapy.
- **NOTE: patients must stop taking antacids, PPIs, H2 antagonists or bismuth preparations for 2 weeks prior to test.**
- Follow-up endoscopy should be performed at a minimum of 6, 12 and 24 months and thereafter at the discretion of the clinician. If possible, the procedures should be performed by the same endoscopist.
- The area of previous abnormality should be photographed. Multiple biopsies should be performed from the area of previous abnormality and submitted for histological examination.
- There are no uniform criteria for the definition of histological remission.
- Complete histological remission can take >12 months.

Note that some retrospective studies have identified a small increase in the risk of gastric cancer in patients with a history of gastric MALT lymphoma; gastro-intestinal symptoms should be investigated promptly in any patient with a history of this disease.

*(b) Other MZL*

- Directed by individual clinical circumstances
- Follow-up usually every 3 months for first year and then every 6 months.

## 12 Hairy Cell Leukaemia

### 12.1 Introduction

Hairy cell leukaemia (HCL) is a rare disorder (2% of all haematological malignancies). Median age is late 50s and it is four times more common in males than females. The clinical course is extremely indolent. Unusual para-neoplastic phenomena can occur.

The majority of patients present with pancytopenia and splenomegaly. A monocytopenia is characteristic.

### 12.2 Investigation and diagnosis

#### 12.2.1 Evaluation at presentation

- History of infections, B symptoms: weight loss and night sweats
- PS
- Physical examination for splenomegaly
- FBC + PBF
- Sample sent to HMDS for diagnostic immunophenotype.
- Further tests performed at diagnosis include: biochemistry, LDH, Immunoglobulins, B2M, viral serology.

#### 12.2.2 Diagnosis of HCL

- Examination of the peripheral blood film normally shows characteristic hairy cells (but the count may be low).
- Four immunophenotypic markers relatively specific for hairy cells can be used: CD11c, CD25, CD103 and CD123. A score of 4/4 is diagnostic.
- A definitive diagnosis requires a bone marrow biopsy. Confirmation of the nature of the infiltration is obtained by immunocytochemistry using CD20 and/or DBA44.
- Good quality trephine biopsies are required not only for diagnosis but also for monitoring response to treatment.
- BRAF is mutated in almost 100% of classical HCL cases. In cases where the diagnosis is in doubt this can be confirmatory but does not otherwise influence management.

- Abdominal CT scan or ultrasound is required at diagnosis to assess spleen size and identify patients with large abdominal nodes.

### 12.2.3 Staging

There is no recognised staging system.

### 12.2.4 Prognosis

- There are no currently recognised prognostic markers.
- There is a suggestion that patients presenting with bulky abdominal nodes and those with more severe anaemia and/or thrombocytopenia have slightly less good outcome.
- Any cases which do not have BRAF mutations or which have IgVH 3-34 usage have poorer outcome.
- HCL-v is an entirely separate disease (now included with the group of splenic lymphomas in WHO), which presents with high WBC, has a different immunophenotype, is BRAF negative and has a poorer outcome than HCL.

## 12.3 Service configuration

- All newly diagnosed cases need to be registered through the MDT, even if only for W&W management plan.
- Any patient requiring therapy, either initial or subsequent treatments, should be discussed in the MDT and considered for suitable clinical trials.

## 12.4 Management of disease-related complications

See the [CLL guidelines](#) as very similar.

## 12.5 Treatment

### 12.5.1 Indications for treatment

- Anaemia (<100 g/l)
- Thrombocytopenia (<100 x 10<sup>9</sup>/L)
- Neutropenia (<0.5)
- Bulky lymphadenopathy/splenomegaly
- Systemic symptoms.

### 12.5.2 Watch and wait

Rarely patients are asymptomatic and, in the absence of the above criteria, W&W is reasonable.

### 12.5.3 First-line therapy

Most patients will require therapy to correct the cytopenias and the associated problems of anaemia, infections and bleeding.

The mainstay of the treatment of HCL comprises the two nucleoside analogues pentostatin and cladribine. Both agents induce a high rate (>80%) of complete remissions which, in the majority of

patients, are prolonged; median DFS for patients treated with pentostatin is 15 years in our series (N=250), with OS at 10 years of 97%. The majority of relapsed patients achieve second remissions when re-treated. Survival is better for patients achieving CR than in those reaching PR. Both pentostatin and cladribine are well tolerated and the only long-term effect is lymphopenia.

### *Regimens*

- Pentostatin (deoxycoformycin) is given by injection every 2 weeks. Usual dose 4 mg/m<sup>2</sup>. Dose reduce/omit if low GFR. Usually treat to max response plus 2. Most patients receive 8–10 injections. Usually assess BM trephine after 8 and if still involved continue for a further 4 injections before repeating.
- 2CDA (cladribine) is given by subcutaneous injection (daily 0.14 mg/kg x 5), BM trephine assessment approximately 3 months after completing treatment. If residual disease is present then give a second cycle of 2CDA.
- Splenectomy is sometimes indicated in refractory cases with massive splenomegaly or for those unable to receive standard chemotherapy.
- Rituximab is not as effective as a single agent but may be useful in frail patients considered unfit for PA therapy.
- Interferon alpha (3MU 3x/w) is very rarely used but may be helpful in patients with profound pancytopenia and infection to improve their counts prior to PA therapy.
- **Monitor response** by blood counts, immunophenotyping of peripheral blood and BM, BM trephine biopsy with immunocytochemistry and abdominal CT (if previously abnormal).

### **12.5.4 Treatment for relapsed/refractory patients**

- Most patients relapse after >5 years in remission and can be re-treated with the same or the alternative PA; subsequent remissions tend to be less durable than the first.
- Patients who fail to achieve a good initial remission or who relapse in <5 years should receive PA + rituximab (375 mg/m<sup>2</sup> x 6–8).
- Very refractory patients should be entered into clinical trials where possible or referred to centres with a specialist interest for advice. The BRAF inhibitor (vemurafenib) has been shown to be effective but responses appear short-lived.

### **12.6 Supportive care**

- Patients receiving purine analogue therapy require pneumocystis prophylaxis with co-trimoxazole (480mg tablet daily), or nebulised pentamidine if allergic to co-trimoxazole. Acyclovir prophylaxis (400 mg BD) against herpes zoster is also recommended. Both should be given during therapy and for up to 6 months afterwards.
- Growth factors, e.g. G-CSF, could also be used to treat neutropenia (<0.5 x 10<sup>9</sup>/L) before, during and/or after the use of either pentostatin or cladribine.
- All patients who have received these drugs should have irradiated blood products indefinitely.
- See [section 6](#) for general supportive care guidance.

## 13 Mantle Cell Lymphoma

### 13.1 Introduction

Mantle cell lymphoma (MCL) is a rare B-NHL with an incidence of 0.5 per 100,000 in the Western world. The median age at presentation is 70 with a male to female ratio of 2–3:1.

Most patients present with advanced stage disease with bone marrow involvement. The gastrointestinal tract is a common site of involvement and approximately a third of patients present with circulating disease in the peripheral blood. CNS involvement has been described in MCL (cumulative incidence approximately 4%) and is more frequent with blastoid morphology and advanced disease.

### 13.2 Investigation and diagnosis

#### 13.2.1 Evaluation at presentation

- B symptoms
- PS (ECOG)
- Physical examination for lymphadenopathy and organomegaly
- FBC+PBF
- Sample to HMDS for diagnostic immunophenotype
- Further tests performed at diagnosis include:
  - Biochemistry
  - LDH
  - Immunoglobulins
  - B2M
  - Viral serology
- CT/PET-CT
- Persistent GI symptoms at presentation should be investigated with OGD or colonoscopy
- MRI +/- lumbar puncture for CSF analysis if suspicion of CSF involvement.

#### 13.2.2 Diagnosis of MCL

- Morphologically, small to medium sized lymphocytes with irregular nuclear contours. Blastoid morphology (about 20% of cases at diagnosis) is recognised by an increase in nuclear size and chromatin dispersal with prominent nucleoli.
- MCL cells express a mature B cell phenotype with expression of CD19, CD20, CD22 and CD79a. CD5 is expressed in the vast majority of cases but, in contrast to CLL, CD20 expression is strong, FMC7 is expressed and CD23 is usually absent.
- The diagnostic hallmark is t(11;14) with over-expression of cyclin D1, but approximately 6% of cases are negative for this translocation and over-express cyclin D2, D3 or E.

CT scan and bone marrow examination are required for staging at diagnosis.

### 13.2.3 Staging

Staging is according to the modified Ann Arbor staging.

Stage	Prognostic groups
Stage I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)
Stage II	Involvement of two or more lymph node regions (number to be stated) on the same side of the diaphragm (II) or localised involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) which may also be accompanied by localised involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIISE)
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement. Organ should be identified by symbols

A – No symptoms  
 B – Fever, drenching night sweats, loss of more than 10% of body weight over 6 months  
 X: Bulky disease: >1/3 mediastinum at the widest point; >10cm maximum diameter of nodal mass  
 E: Involvement of single, contiguous or proximal, extra nodal site

### 13.2.4 Prognosis

- The mantle cell lymphoma international prognostic index (MIPI) is calculated using four independent prognostic factors – age, ECOG status, LDH and leucocyte count. Online calculator – [www.european-mcl.net/en/clinical\\_mipi.php](http://www.european-mcl.net/en/clinical_mipi.php).

	MIPI	Median OS
Low risk	<5.7	Not reached
Intermediate risk	5.7–6.2	54 months
High risk	>6.2	29 months

- Ki67 has been shown to be an independent prognostic marker in MCL and the 'biological' MIPI (MIPIb) incorporating the Ki67 proliferation index may be a more powerful predictor but requires standardisation of Ki67 scoring.

Ki67	Median survival
<10%	42 mths
11–40%	30 mths
>40%	15 mths

Source: Tiemann *et al*, 2005.



## 13.3 Treatment

### 13.3.1 Watch and wait

Most patients with MCL are symptomatic at presentation but, in the absence of symptoms, watch and wait is a reasonable approach and has been shown not to have a negative impact on survival. Indeed, a small proportion of patients have 'indolent' MCL which can be managed expectantly, sometimes for years. These patients generally present with isolated lymphocytosis with or without splenomegaly. Molecular markers (e.g. SOX11) to identify this group of patients should be done where possible.

### 13.3.2 First-line therapy

All patients should be considered for entry into a clinical trial.

- Patients fit for high-dose therapy should be treated with one of two high dose Ara-c containing induction regimens followed by consolidation with a high dose regimen such as BEAM or LEAM and an autologous stem cell transplant (ASCT):

1. NORDIC MCL2 protocol – R-maxiCHOP alternating with R-HDAra-C.

2. R-CHOP(21)x3 alternating with R-DHAPx3 (Delarue, 2013, and European 'MCL younger' trial).

Rituximab maintenance should be considered post autologous SCT (LyMa trial).

Consideration should be given to allogeneic stem cell transplantation in CR1 for very high-risk patients (e.g. high MIPI) instead of autologous transplantation. Wherever possible, allogeneic transplantation for MCL should be done in the context of a clinical trial

- Patients not fit for high-dose therapy should be treated with R-CHOP x6 followed by rituximab maintenance (Kluin-Nelemans, 2012). Alternative induction regimens that could be considered in less fit patients or those unable to tolerate CHOP include R-BAC (rituximab, bendamustine, cytarabine), R-bendamustine, VR-CAP (Robak, 2015), and R-chlorambucil.
- CNS prophylaxis may be justified in patients with blastoid, advanced stage disease.

### 13.3.3 Treatment for relapsed/refractory patients

All patients should be considered for entry into a clinical trial.

- In younger/fitter patients consideration should be given to salvage treatment with a BTK inhibitor (e.g. Ibrutinib) followed by LEAM ASCT consolidation (if they did not receive this upfront) or by allogeneic SCT if there is a suitable donor. Alternatives include R-BAC, R-Gem-P, R-DHAP, R-bendamustine or R-bortezomib +/- cytarabine (R-HAD + B). Patients relapsing within 6 months of treatment with rituximab are unlikely to benefit from addition of this to their salvage regimen.
- In older patients, treatment with Ibrutinib should be considered. Alternative regimens include R-bendamustine, R-BAC, R-FC, R-bortezomib, and R-chlorambucil. Patients relapsing within 6 months of treatment with rituximab are unlikely to benefit from addition of this to their salvage regimen.

- Novel agents: Venetoclax combination therapy shows promise (currently not funded). Lenalidomide is active in relapsed MCL (not funded). Idelalisib has less activity in MCL but broader PI3K inhibitors may be more promising.
- **Splenectomy** may be useful in selected patients, especially those with leukaemic presentation and splenomegaly with no nodal disease.
- **Radiotherapy** can be useful in localised disease, usually for palliation.
- **Allogeneic HSCT** should be considered for suitable patients.

#### 13.4 Supportive care

- Acyclovir prophylaxis (400 mg BD) is recommended for all patients. Co-trimoxazole prophylaxis is recommended in addition for patients receiving purine analogues. Both should be given during therapy and for up to 6 months afterwards. See [section 6](#) for general supportive care guidance.

## 14 Burkitt Lymphoma

### 14.1 Introduction

Adult Burkitt lymphoma (BL) can be endemic, sporadic or associated with immunodeficiency. Endemic BL is invariably EBV-positive and occurs in equatorial Africa with a peak incidence in childhood (jaw, facial bones and GI tract). Sporadic BL has a median age of 30 with a male preponderance (2–3:1). The incidence is approximately 2.5 cases per million per annum.

### 14.2 Investigation and diagnosis

#### 14.2.1 Clinical features

- Rapidly progressive bulky nodal and/or extranodal disease with frequent bone marrow, intestinal tract and leptomeningeal disease.
- Investigations must be completed rapidly as treatment should commence within 48 hours of diagnosis.
- FBC and differential, ESR, CRP.
- Clotting screen.
- U&Es, LFTs, uric acid, Ca, PO<sub>4</sub>, B<sub>2</sub>M, LDH.
- Immunoglobulin profile, serum protein electrophoresis.
- Full hepatitis B profile: Hep B S Ab, Hep B S Ag, Hep B c Ab, Hep C Ab.
- HIV Ab with counselling and consent.
- Lumbar puncture with CSF for cytology, flow cytometry ± PCR for IgH gene rearrangement if suspicious cells seen.
- MRI scan if spinal cord involvement/CNS suspected/may be used in pregnancy/patient allergic to iodine contrast.
- PET/CT (high sensitivity no false negatives) but do not delay treatment to obtain.
- Preferably an **excision lymph node biopsy by designated surgeons** (or in some circumstances a core biopsy of an inaccessible lymph node or extra lymphatic organ or in rare cases requiring urgent medical treatment). Fine needle aspiration is **not** adequate for the diagnosis.
- The biopsy should be examined by a haematopathologist. Diagnostic criteria for BL and its variants have changed considerably over time.

## 14.2.2 Staging

The modified Ann Arbor staging is most frequently used in adults.

Stage	Prognostic groups
Stage I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)
Stage II	Involvement of two or more lymph node regions (number to be stated) on the same side of the diaphragm (II) or localised involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) which may also be accompanied by localised involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIISE)
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement. Organ should be identified by symbols

A – No symptoms  
 B – Fever, drenching night sweats, loss of more than 10% of body weight over 6 months  
 X: Bulky disease: >1/3 mediastinum at the widest point; >10cm maximum diameter of nodal mass  
 E: Involvement of single, contiguous or proximal, extra nodal site

## 14.2.3 Further tests in specific circumstances

- Left ventricular ejection fraction estimation in patients with cardiac history/risk factors (hypertension/DM/IHD), elderly >65 years/frail where anthracyclines are being considered
- Pulmonary function tests
- Sperm count and cryopreservation if appropriate
- ENT examination.

## 14.2.4 Prognostic factors

Adverse outcome in patients >40 years, advanced stage, especially bone marrow and CNS involvement, raised LDH, failure to achieve a CR in 6–8 weeks.

## 14.2.5 Pathology

Morphology shows a diffuse monotonous infiltrate of medium sized cell, round nuclei, clumped chromatin, basophilic cytoplasm with lipid vacuoles and a mitotic index of greater than 95%.

The cells are of germinal centre origin and express B cell markers (CD19, 20, 22), CD10 and BCL-6 and endemic BL, CD21. Cells are negative for CD5, CD23, tdt, bcl-2 (weak), CD34 and light chain restricted immunoglobulin.

Translocation involving MYC ((8q24), t(8:14), t(2:8)) is present in 90% by FISH, with EBV in a variable proportion.

Importantly the presence of MYC is not diagnostic of BL and is seen in 10% of DLBCL and 30–50% of BL unclassified (cases intermediate between BL and DLBCL). Frequently with breakpoints in BCL6 or t(14:18) as well as MYC so called ‘double hit’ lymphomas.

Greater diagnostic precision can be achieved with gene profiling (high expression of GC B cell genes and low expression of MHC 1 and NFkB pathway genes) but outside of clinical trials it is not yet routinely available.

### 14.2.6 Imaging

Baseline contrast-enhanced CT with PET if available. End of treatment PET/CT.

## 14.3 Management of specific disease-related complications

Specific disease-related complications such as leptomeningeal involvement and spinal cord compression should be managed according to local treatment centre policy.

## 14.4 Treatment

Treatment for BL and its variants should be prompt (<48 hours) with adequate supportive care. Tumour lysis should be managed with rigorous hydration and rasburicase.

All new and relapsing cases should be discussed at the next local network MDT meeting with central review by a specialist haematopathologist.

Treatment facilities to administer induction treatment should be BSCH level 3. Patients with less than a CR or with chemosensitive relapse should be referred to a JACIE-accredited SCT unit for consolidation autograft.

Rapid access pathways should be in place to allow both primary care and specialist medical teams to urgently refer suspected cases with transfer once stable to a level 3 centre.

Brief intense chemotherapy is the treatment of choice. Patients are managed according to risk groups. The CNS is frequently involved.

Low risk patients should receive CODOX-M x3 cycles – patients must have at least three of the following:

- Normal LDH level
- WHO performance status 0–1
- Ann Arbor stage I–II
- Number of extranodal sites (e.g. bone marrow, GI tract, CNS)  $\leq 1$ .

All other patients considered high risk/patients under 60 years should receive R-CODOX-M/R-IVAC x2. **Tumour lysis is common and patients should receive rasburicase** (see [Annex 1](#) and [Annex 2](#)).

Patients who fail to achieve a CR or chemosensitive relapse should be referred for consolidation with an autologous SCT. Allografting is not indicated.

Elderly patients should be treated with the most intensive treatment they can tolerate following careful assessment and presentation and continual re-evaluation of co-morbidities, toxicities and functional capacity.

Patients over 60 years should be considered for the age-adjusted protocol of R-CODOX-M/R-IVAC. Cases should be considered on an individual basis. Good results in the elderly and those with HIV have been reported with DA-EPOCH-R and GMALL (omission of HD cytosine arabinoside and methotrexate reduced to 500 mg/m<sup>2</sup>) for those not suitable for intensive therapy. Patients unable to tolerate these regimens consider standard RCHOP.

Intrathecal prophylaxis should be given when CNS penetrative drugs are not included in the regimen.

## 14.5 End of treatment information

Short duration, intense chemotherapy cures 90% of low-risk and 60–80% of high-risk patients. Relapse, if it occurs, is usually within a year, with cure defined as remission of >2 years. Patients should be aware of possible symptoms or relapse/progression and given details to contact the medical team urgently in these occurrences. Information on possible symptoms and contact details should be included in the treatment summary (see [section 7: End of Treatment Information](#)).

## 14.6 Specific or miscellaneous considerations

- HIV-positive patients usually have good CD4 counts and should be managed with antiretroviral therapy concurrently with aggressive short duration chemotherapy. More mucositis and more severe infections are seen.
- Patients in the TYA age group should be referred for discussion in a specialist TYA MDT with the option of being treated in a TYAC. See [section 3.1](#) for more details. Consideration should be given to alternative age-appropriate/adolescent protocols, e.g. SFOP LMB.
- Patients with Burkitt-like lymphoma and BL unclassifiable (feature intermediate between DLBCL and Burkitts) do poorly with RCHOP and where possible should be treated as BL.

## 15 Peripheral T-Cell Lymphomas and Leukaemias

### 15.1 Introduction

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of rare malignancies accounting for approximately 10–12% of all lymphoid neoplasms. Most have an aggressive clinical behaviour and, apart from anaplastic large cell lymphoma (ALCL), a poor response to conventional chemotherapy with only 30% survival at 3 years. Patients often present with disease at extranodal sites and poor PS.

#### 15.1.1 WHO classification

##### (a) *Nodal*

- Peripheral T-cell lymphoma, unspecified
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma (ALCL) (ALK+, ALK-, primary cutaneous)
- Adult T-cell lymphoma/leukaemia.

##### (b) *Extranodal*

- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma.

##### (c) *Cutaneous*

- Mycosis fungoides/Sézary syndrome
- Lymphomatoid papulosis.

### 15.2 Clinical presentation and referral pathways

#### 15.2.1 Presentation

Patients usually present with palpable lymphadenopathy and systemic symptoms. Presentation at extranodal sites is common and patients may therefore be under the care of other hospital specialties before the histological diagnosis is confirmed.

#### 15.2.2 Referral pathways

Referral from primary care should be made using the 2-week wait referral form to rapid access neck lump diagnostic clinics. Presentation via other specialties can delay diagnosis.

### 15.3 Investigation and diagnosis

#### 15.3.1 Diagnosis

Diagnosis is based on examination of adequate histological material from tissue biopsy 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.

### 15.3.2 Investigations

- FBC, renal and liver profile, LDH, Igs, Beta2 microglobulin
- Virology: hepatitis B&C, HIV, EBV (including EBV PCR), HTLV1
- Strongyloides serology in ATLL
- BM aspirate and trephine biopsy
- CT-NCAP (PET)
- Lumbar puncture/MRI of brain is not routinely required in the absence of CNS symptoms or signs.

### 15.3.3 Staging

Staging is according to the modified Ann Arbor staging:

Stage	Prognostic groups
<b>Stage I</b>	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)
<b>Stage II</b>	Involvement of two or more lymph node regions (number to be stated) on the same side of the diaphragm (II) or localised involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE)
<b>Stage III</b>	Involvement of lymph node regions on both sides of the diaphragm (III) which may also be accompanied by localised involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIISE)
<b>Stage IV</b>	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement. Organ should be identified by symbols
<p>A – No symptoms            B – Fever, drenching night sweats, loss of more than 10% of body weight over 6 months  <b>X</b>: Bulky disease: &gt;1/3 mediastinum at the widest point; &gt;10cm maximum diameter of nodal mass  <b>E</b>: Involvement of single, contiguous or proximal, extra nodal site</p>	

### 15.3.4 Prognosis

The IPI is useful in PTCL-NOS but less so in the extranodal subtypes. Specific T-cell scores have been devised (PIT).

## 15.4 Service configuration

The T-cell malignancies are rare and often complex diseases. Diagnosis and management should be discussed in a network multidisciplinary team meeting and those patients requiring treatment should generally be referred to a cancer centre or tertiary centre with specialist expertise.



## 15.5 Treatment

Where possible patients should be entered into clinical trials. Patients often have very aggressive disease and treatment delays should be avoided (use of GCSF may be indicated).

Infection risk is high because of immunosuppression.

### 15.5.1 Treatment of specific subtypes

#### (a) *PTCL-NOS, AITL*

- Outside trial, CHOP (14 or 21) x 6 remains the standard first-line therapy. Phase 2 data suggest that strong consideration should be given to consolidation with auto- (or allogeneic) HSCT in first remission
- Alternative induction therapies include: CHOEP, GEM-P, ICE, Newcastle (NCRI/SNLG).
- Relapsed or refractory disease should be treated with remission induction therapy (preferably within a clinical trial) and patients with chemosensitive disease considered for allo-HSCT or novel therapies within a trial setting. Outcome for patients with relapsed/refractory disease is extremely poor.
- In the absence of a licenced agent there is insufficient evidence to recommend the use of a specific non-chemotherapy agent. Brentuximab vedotin has good activity in other CD30 + PTCL (not funded).
- In AITL the timing and selection of therapy depend on clinical presentation and prognostic features. Rare spontaneous regressions can occur. Alternative treatments with some efficacy include steroids, purine analogues (FC), immunomodulatory drugs (thalidomide, lenalidomide, ciclosporin A), azacytidine and HDAC inhibitors (belinostat and chidamide).
- CNS involvement is rare but may be considered when >1 ENS is involved

#### (b) *ALCL*

- ALCL ALK+ and ALK- should receive Brentuximab-CHP where possible (currently not funded). Otherwise six cycles of CHOP14 or 21 chemotherapy. There is some evidence to suggest that younger patients with this subtype benefit from the addition of etoposide. Consideration should be given for ASCT in CR1 for ALK- ALCL and high risk ALK+ ALCL.
- At first relapse patients should receive Brentuximab if BV naïve or BV sensitive. BV resistant patients should receive combination chemotherapy and those with chemosensitive disease considered for allo/auto-HSCT or novel therapies within a trial setting. Outcome for patients with relapsed/refractory disease is extremely poor.
- Primary anaplastic large cell lymphoma associated with breast implants (BIA-ALCL); Stage 1 disease should be managed with surgery alone. Adjuvant chemotherapy may be required for more invasive disease and treated as systemic ALCL with brentuximab if available.
- Primary cutaneous ALCL (ALK-neg) should be managed with surgical excision and / or radiotherapy for localised disease. Combination chemotherapy or brentuximab should be reserved for patients with extensive cutaneous disease or systemic progression.
- Lymphomatoid papulosis is a CD30+ cutaneous disease which is sometimes mistaken for primary cutaneous ALCL. Treatment for LyP ranges from an expectant policy for patients with

limited disease to phototherapy, radiotherapy, low-dose methotrexate or interferon-alpha for patients with extensive disease. The use of conventional chemotherapy is not indicated in the management of lymphomatoid papulosis.

- 

(c) ATLL

- Hypercalcaemia is common at diagnosis and requires vigorous management (see management of complications).
- Exclude co-infection with strongyloides prior to commencing therapy. An intensified Strongyloides eradication protocol is recommended for strongyloides positive HTLV-1 carriers, available from HTLV service at St Mary's ([imperial.htlv@nhs.net](mailto:imperial.htlv@nhs.net)).
- Antimicrobial prophylaxis with septrin, fluconazole and acyclovir for all patients on chemotherapy, and continue septrin and acyclovir for those on ZDV/IFN maintenance.
- Refer/discuss patients and/or relatives with newly detected HTLV to the service at St Mary's who offer proviral load monitoring, MRD detection, clinical trials etc. Counselling and screening of relatives/partners is essential. Relatives of ATL cases are at high risk of ATL and other complications ([imperial.htlv@nhs.net](mailto:imperial.htlv@nhs.net)). Forms for molecular monitoring and patient information sheets available at [www.htlv.eu](http://www.htlv.eu)
- Symptomatic Smouldering and chronic:
  - Zidovudine (ZDV) and interferon- $\alpha$  indefinitely (or guided by MRD)
  - If progressive disease switch to CHOP followed by allogeneic SCT in eligible patients.
- Lymphoma type:
  - Induction with CHOP or alternative multi-agent regimen plus G-CSF with concurrent ZDV + interferon- $\alpha$
  - ZDV + interferon- $\alpha$  maintenance
  - Allogeneic transplant in 1<sup>st</sup> CR for eligible patients.
- Leukaemia (acute) type:
  - Induction with high dose antiretroviral therapy alone (ZDV + interferon- $\alpha$ ), switch to CHOP-like regimen if no response
  - OR If significant lymphadenopathy induction with CHOP or alternative multi-agent regimen plus G-CSF + concurrent ZDV + interferon- $\alpha$
  - Allo HSCT in 1st CR for eligible patients
  - OR ZDV + interferon- $\alpha$  maintenance +/- MoAbs
- - OR oral etoposide containing maintenance chemotherapy (e.g. PEP-C regimen)
  - OR consolidation with novel agents, e.g. arsenic trioxide,  $\alpha$ IFN; proteasome inhibitor in clinical trials.
- CNS prophylaxis should be considered for all individuals with acute or lymphoma subtypes

*(d) Extranodal NK/T cell lymphoma / leukaemia*

- A staging PET/CT is preferred to identify occult extranodal disease sites because of the critical need to distinguish localised and advanced stage disease. In localised disease an MRI is helpful to assess local extent
- Demonstration of EBV virus in the biopsy is important diagnostically and should be confirmed using EBER ISH. Monitoring EBV PCR is useful to assess response/relapse.
- Patients with localised disease should receive asparaginase containing chemotherapy such as LVDP (Jiang et al 2017), GELOX (Wang et al), DeVIC (Yamaguchi 2012 and 2016) with concurrent, sequential or sandwich radiation of >50Gy.
- Multiagent asparaginase-containing regimens such as SMILE (Steroids, Methotrexate, Ifosfamide, L-asparaginase and Etoposide), (Yamaguchi *et al*, 2011, Kong *et al*, 2012), DDGP (Li et al, 2016), ASpMetDex in the less fit (Jaccard et al), should be considered in disseminated first-line and in relapsed or refractory disease.
- High-dose therapy should be considered in CR1 for advanced stage disease.

*(e) Enteropathy-associated T-cell lymphoma (EATL) and Monomorphic epitheliotropic intestinal T-cell lymphoma (MEATL)*

- Indolent T cell lymphoproliferative disorder of the gastrointestinal tract is managed with watchful waiting and must be differentiated from EATL and MEATL.
- It is important to liaise with an experienced gastroenterologist to assist with biopsy, staging and follow-up, and to manage nutritional problems.
- Assigning a conventional IPI score is of limited value as there is no good prognostic group and most cases are stage I–IIe.
- A more intensive approach such as the Newcastle (NCRI/SNLG) protocol or similarly intensive therapy is a reasonable option in fitter patients. CHOP-like therapy, followed by an autograft in first CR, remains a common approach outside a trial. Half dose CHOP-like treatment should be considered with cycle 1 due to early treatment related mortality.
- Nutrition is a major issue in managing these patients and dietetic/gastroenterology advice is essential at all stages of treatment and follow-up.

*(f) Hepato-splenic T-cell lymphoma*

- Often occurs in younger males, can be associated with a history of chronic inflammatory disorders and follows an aggressive clinical course.
- Outcomes are extremely poor with conventional treatment. CHOP is insufficient therapy.
- Autologous or allogeneic bone marrow transplantation could be considered in younger fit patients achieving CR.

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

- Very rare.
- This is not a universally aggressive disease and careful initial assessment and observation should be undertaken before committing to treatment.

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

#### (h) *Cutaneous T cell lymphoma (CTCL)*

Communication and collaboration with dermatology and clinical oncology are vital for optimal patient management. It is therefore recommended that all patients are referred to a specialist centre such as St John's Institute of Dermatology with access to appropriate expertise and all therapeutic modalities.

In the early stages, mycosis fungoides (MF) may be controlled by skin directed therapy (SDT) alone, such as PUVA, topical chemotherapy, bexarotene and electron beam irradiation. A variety of treatment modalities have been used to treat more advanced CTCL, with varying success.

#### • **Initial assessment**

- Repeated skin biopsies classified according to the WHO classification.
- Staging CT scans (except MF stage IA/IB and LyP).
- PB for WBC, lymphocyte and Sézary cell counts, serum LDH, liver and renal function, lymphocyte subsets, CD4:CD8 ratios, HTLV-I serology and TCR gene analysis.
- Bone marrow aspirate/trephine biopsies MF stage IIB or above and CTCL variants, not LyP.
- Lymph node biopsy if rapidly enlarging node or advanced clinical stage and palpable adenopathy (>1.5 cm).
- Staging: TNM, Bunn and Lambert.
- Review in MDT stages IIA–IVB. Membership to include dermato-pathologist, dermatologist, clinical oncologist, haemato-oncologist, palliative care.

#### **Treatment algorithm for MF/SS**

<b>Prognostic group (stage)</b>	<b>1st line</b>	<b>2nd line</b>	<b>Third line</b>
(IA–IIA)	Expectant or SDT	Bexarotene, IFN, TSEB	Clinical trials or IIB options
(IIB)	SDT; TSEB, Bexarotene, IFN	Brentuximab, Mogamulizumab Clinical trials	Chemotherapy RIC-AlloSCT
Stage III erythrodermic	SDT, MTX; ECP/IFN/Bex ; trials	Brentuximab; Alemtuzumab; Mogamulizumab	Chemotherapy TSEB; RIC-AlloSCT
	SDT; EBRT;	Brentuximab, Bexarotene;	Clinical trials;

(IIB/IVA2, IVB)	chemotherapy; trials	Mogamulizumab if possible; RIC-AlloSCT:clinical trials; palliative therapy	RIC-AlloSCT
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Abbreviations used in table:

SDT – skin directed therapy: topical therapy; phototherapy (TLO1/PUVA); radiotherapy; TSEB – total skin electron beam therapy; IFN – alpha interferon; Bex – bexarotene; HDACi – histone deacetylase inhibitors (vorinostat/romidepsin)\*; EBRT, external beam radiotherapy with photons or electrons for lymph node, soft tissue or visceral lymphoma; ECP – extracorporeal photopheresis; MTX – methotrexate; Ontak – Denileukin difititox; RIC-AlloSCT – reduced intensity conditioned allogeneic stem cell transplant.

## 16 T-cell Prolymphocytic Leukaemia (T-PLL)

### 16.1 Introduction

T-cell prolymphocytic leukaemia (T-PLL) is a rare aggressive disease accounting for <2% of all leukaemias. Usually the response to traditional chemotherapy is poor with a median survival of only 7 months.

### 16.2 Presentation

Patients usually present with rapid onset of symptoms with:

- Splenomegaly (common)
- Marked leucocytosis, usually  $>100 \times 10^9/L$
- Lymphadenopathy is rare (it is more common with B-PLL)
- Systemic disease including rashes (20%), pleural effusions, CNS involvement (-10%).

### 16.3 Investigation and diagnosis

#### 16.3.1 Investigation

- History of infections, B symptoms, weight loss and night sweats
- PS
- Physical examination for lymphadenopathy/splenomegaly/hepatomegaly/skin rash
- FBC and PBF
- Sample sent to HMDS for diagnostic immunophenotype, cytogenetics and molecular genetics (TCR gene rearrangement). Further tests performed at diagnosis include:
  - Biochemistry (including urate and LDH)
  - Serum Immunoglobulins and B2M
  - Viral serology (hepatitis, EBV, CMV, HIV)
- A BM aspirate and trephine biopsy is not necessary to make the diagnosis and can be misleading if PB results are not reported. A BM should be performed pre- and post-treatment to evaluate response
- CT scans are required for initial evaluation and to assess response to treatment
- LN biopsy is only required if there is doubt about the diagnosis.

#### 16.3.2 Staging and prognosis

There are no specific staging or prognostic systems for T-PLL.

### 16.4 Service configuration

- All cases should be discussed at the MDT at presentation and at relapse.
- Since this is a very rare disease, discussion with a centre with a specialist interest is advised.
- Early referral should be made to a transplant centre for consideration of SCT in first remission for eligible patients.

## 16.5 Treatment

### 16.5.1 Watch and wait

A small percentage of patients (15%) may present with an isolated lymphocytosis which can remain stable for a prolonged period. Progression is inevitable and may occur rapidly. Therefore, patients should be monitored closely (q1–2 monthly).

### 16.5.2 First-line therapy

- Intravenous alemtuzumab (30 mg 3x/week) is the most effective treatment in T-PLL and administered as a single agent can achieve response rates of about 90%. Patients should continue on treatment to complete response (12–18 weeks).
- Slow or incomplete responders and those with bulky nodal or extranodal disease may benefit from the addition of a purine analogue, e.g. pentostatin 4 mg/m<sup>2</sup>/week or FC.
- Eligible patients should be referred for consideration of an SCT (allo or auto) in first remission.
- During and after alemtuzumab treatment patients should be monitored weekly until recovery of CD4 counts >200µL and CR and then 1–3 monthly depending on clinical status.

### 16.5.3 Relapsed/refractory disease

- Previously good responders to alemtuzumab who retain expression of CD52 on the T-PLL cells at relapse can be retreated with alemtuzumab.
- Patients refractory to alemtuzumab or CD52-negative have few effective treatment options. Possibilities include: FMC, pentostatin, nelarabine, bendamustine, intensive regimens (mini-BEAM, IVE).
- Eligible patients should be referred for transplant in second remission.

## 16.6 Supportive care

- Infusion reactions with alemtuzumab are common and should be managed with careful use of pre-medication and pethidine to control rigors as needed.
- Patients receiving alemtuzumab and/or purine-analogue containing chemotherapy should receive PCP and herpes prophylaxis. Those receiving alemtuzumab require weekly monitoring for CMV reactivation and pre-emptive treatment with oral valganciclovir or IV ganciclovir/foscarnet if CMV titres rise.
- The use of G-CSF should be considered in patients with prolonged/severe neutropenia to support delivery of therapy.
- Patients who have received PAs or antibodies should have irradiated blood products.
- See [section 6](#) for general supportive care guidance.

## 16.7 Research and clinical trials

- Where possible all eligible patients should be entered into an appropriate clinical trial and consideration should be given to referring a patient to a specialist centre where a suitable trial may be open. For more details see [section 9: Research and Clinical Trials](#).
- Given the rarity of this disorder biobanking of material should be attempted in all cases.

## 17 T-cell Large Granular Lymphocyte Leukaemia and Chronic NK LPD

### 17.1 Introduction

This is a rare disorder accounting for <3% of all cases of small lymphocytic leukaemias. Median age is 55 years and median survival is >10 years.

It consists of two separate entities: 80–90% are mature CD3+/CD8+ T-LGLs; 10–20% have an NK cell phenotype. Both follow a chronic benign clinical course.

### 17.2 Presentation

- Usually an incidental finding on an FBC.
- Cytopenias are characteristic, particularly neutropenia with associated infections, mouth ulcers and fatigue.
- Autoimmune disorders including haemolytic anaemia, red cell aplasia and sometimes thrombocytopenia.
- About one third of patients have a history of rheumatoid arthritis.
- Splenomegaly is common but the lymph nodes and other organs, including skin, are usually not involved.
- An aggressive NK cell leukaemia occurs in young adult males and is characterised by neutropenia, anaemia, and thrombocytopenia accompanied by significant marrow infiltration, splenomegaly and hepatomegaly. It is associated with Epstein–Barr virus and usually follows a rapidly fatal clinical course (see NK/T leukaemia/lymphoma)

### 17.3 Investigations and diagnosis

#### 17.3.1 Investigations

- History of infections, mouth ulcers, B symptoms: weight loss and night sweats.
- PS.
- Physical examination for lymphadenopathy/splenomegaly/hepatomegaly.
- FBC + PBF.
- Sample sent to HMDS for diagnostic immunophenotype and molecular genetics (TCR gene rearrangement).
- Further tests performed at diagnosis include: DAT, reticulocyte count, biochemistry (including urate and LDH), serum Immunoglobulins and B2M, viral serology, auto-immune profile.
- A BM aspirate and trephine biopsy is not always necessary at diagnosis. A BM should be performed pre- and post-treatment to evaluate response.
- CT scans are not required for initial evaluation outside clinical trials but abdominal US may be useful to assess splenic enlargement.
- LN biopsy is only required if there is doubt about the diagnosis.



### 17.3.2 Diagnosis

- Persistent LGL (T or NK) lymphocytosis ( $2\text{--}20 \times 10^9/\text{L}$ ) for  $>6$  months.
- Distinction from normal reactive T-cell populations can be difficult and relies on demonstrating clonality (PCR, cytogenetics, KIR antigens).
- The finding of a clonal T-cell population should be interpreted with caution, and always in the clinical context.
- STAT3 mutations are present in about 40% of cases.

### 17.3.3 Staging and prognosis

No specific systems exist for staging and prognosis.

## 17.4 Service configuration

- All newly diagnosed cases need to be registered through the MDT, even if only for W&W management plan.
- Any patient requiring therapy, either initial or subsequent treatments, should be discussed in the MDT and considered for suitable clinical trials.
- The majority of cases can be managed in local hospitals with facilities for OP monitoring and therapy.

## 17.5 Treatment

### 17.5.1 Watch and wait

- Usually a very indolent disorder, and a third to a half of patients may not require treatment.
- Indications for treatment: symptomatic anaemia ( $<9$  g/dl) and/or the need for transfusion; severe neutropenia ( $< 0.5 \times 10^9/\text{L}$ ) associated with infection; severe thrombocytopenia ( $< 50 \times 10^9/\text{L}$ ); or any combination of these.

### 17.5.2 First-line therapy

There is no well-established therapy.

Options include:

- Weekly low-dose oral methotrexate ( $10 \text{ mg}/\text{m}^2$ ) for at least 3–4 months before assessing response
- Cyclosporin A 100 mg BD (to achieve serum trough of 100–150) for at least 3–4 months before assessing response
- Low dose daily oral cyclophosphamide (50 mg/day)
- Prednisolone and/or growth factors may help to speed initial response but should not be given on prolonged schedules.

### 17.5.3 Relapsed/refractory disease

- Pentostatin 4 mg/m<sup>2</sup> every 2 weeks
- Alemtuzumab for relatively short course of therapy to obtain improvement in cytopenias (4–6 weeks)
- Very rarely patients have aggressive disease/transformation requiring intensive regimens and consideration of SCT.

### 17.6 Management of specific disease-related complications

Infections, autoimmune cytopenias (manage as for CLL see [CLL guidelines](#)).

### 17.7 Follow-up arrangements

Frequency of follow-up is determined by individual clinical circumstances.

## Annex 1: Guideline for the Management of Tumour Lysis Syndrome

To be read in conjunction with [Annex 2: Guidelines for Use of Rasburicase in Adult Haematology and Oncology Patients](#).

Tumour Lysis Syndrome (TLS) is life-threatening. Rapid lysis of tumour cells leads to the release of cellular contents into circulation resulting in hyperkalaemia, hyperphosphataemia, hyperuricaemia and hypocalcaemia which may lead to acute oliguric renal failure and cardiac arrhythmias. TLS can occur spontaneously in tumours with a very high proliferative rate, and/or during induction treatment. It can be classified as laboratory TLS (no clinical manifestations) or clinical TLS (life-threatening clinical abnormalities). Symptoms during TLS/rasburicase include fever, haemolysis, headaches, vomiting, diarrhoea, rash and hypersensitivity reactions.

### Prevention of TLS

1. Standard care is hydration and allopurinol and these help prevent TLS
2. Check urate, renal function and LDH prior to starting chemotherapy and hydrate with 3L/m<sup>2</sup> over 24 hours
3. For high risk patients rasburicase should be considered.

**Management (see separate rasburicase protocol):** Rasburicase is to be used immediately prior to and during treatment-induction for the indications below and when authorised by a consultant haematologist.

**TLS Screen is to be ordered 1–4 times per day according to patient’s clinical condition until resolves:** urea, creatinine, uric acid, phosphate, potassium, corrected calcium and LDH (FBC if AML/ALL/CML/MPN).

Risk Group	Diagnosis	Preventative Strategies
<b>High</b>	Burkitt lymphoma Burkitt-type ALL AML or ALL with WBC >100 x 10 <sup>9</sup> /L	1. IVF (~3L/m <sup>2</sup> /day, to maintain UOP >100ml/m <sup>2</sup> /hr) or aggressive hydration as per chemotherapy protocols. 2. Rasburicase* as per rasburicase protocol
<b>Moderate</b>	AML with WBC > 50 x 10 <sup>9</sup> /L Other ALL High grade NHL with bulky disease CML accelerated/blast phase, or where rapid response to therapy expected	1. IVF (~3L/m <sup>2</sup> /day, to maintain UOP >100ml/m <sup>2</sup> /hr) or aggressive hydration as per chemotherapy protocols. 2. Rasburicase* as per rasburicase protocol
<b>Minor</b>	Other AML Myeloma Other lymphoma/CLL Other CML and MPN	Use allopurinol. Use rasburicase* where clinically indicated (high risk): High LDH (>ULN) Renal failure High proliferation index High uric acid (>420 umol/L or 7mg/ml)

\* No dose adjustment in renal/hepatic impairment. Ensure normal G6PD level prior to rasburicase (if low, use aggressive hydration & allopurinol).

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## Annex 2: Guidelines for Use of Rasburicase in Adult Haematology and Oncology Patients

### Criteria for use

Rasburicase may be used only for the following indications, when authorised by a consultant haematologist or oncologist:

Urate oxidase (rasburicase) is an enzyme which catalyses the oxidation of uric acid to allantoin, which is more easily excreted in the urine.

### Used in the treatment of:

- hyperuricaemia associated with high grade haematological malignancies
- prevention of complications of tumour lysis syndrome.

### Indications (see also separate guideline):

- Induction or salvage therapy of AML, ALL, high grade lymphoma, high grade multiple myeloma with
  - High LDH (>ULN)
  - Renal failure
  - High proliferation index (Ki67>80%; consider if Ki67>50%)
  - High uric acid (>420 umol/L or 7mg/ml)

Further to the above, consider using rasburicase in those patients unable to tolerate aggressive hydration.

### Protocol for use:

1. Ensure patient (male or female) is G6PD negative prior to use (if positive, use aggressive hydration with allopurinol – consider higher doses based on risk of TLS and creat level).
2. Ensure aggressive hydration as per chemotherapy protocols.
3. At initiation of treatment, for uric acid levels of:
  - a) <420 umol/L (7mg/L), give a single 3mg dose of rasburicase.
  - b) >420 umol/L (7mg/L), give a single 6mg dose of rasburicase.
4. Local policies should be followed with regard to collecting blood samples and laboratory monitoring.
5. Start allopurinol as per protocols the morning after rasburicase given.
6. Measure uric acid levels as per tumour lysis (TLS) protocols and at least daily until TLS resolved.
7. During TLS monitoring, if uric acid levels >20 umol/L (>0.3 mg/L), or renal failure worsens, give another 1.5–6 mg rasburicase, as indicated by level and clinical parameters of TLS.

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### Special warnings and precautions for use

Allergic reactions may occur with this product, patients should be closely monitored and full resuscitation facilities should be at hand. Should any serious allergic or anaphylactic reaction occur treatment should be immediately discontinued and appropriate resuscitation given.

Caution should be exercised in patients with a history of atopic allergies.

Administration of rasburicase decreases serum uric acid to below normal levels, **but has no direct effect in reversing hyperphosphataemia, hyperkalaemia and hypocalcaemia. If severe these abnormalities should be corrected following standard treatment guidelines.**

There are limited data available to recommend the sequential use of rasburicase and allopurinol.

To ensure accurate measurement of uric acid plasma level during treatment with rasburicase, a strict sample handling procedure must be followed to minimise ex vivo degradation of the analyte. Local policies should be followed with regard to collecting blood samples and laboratory monitoring.

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