# Clinical Guidelines for Lymphoid Diseases – Lymphoma and CLL

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<tr>
<th>Reference Number</th>
<th>Version</th>
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<th>Author(s) Name and Job Title</th>
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<td>3</td>
<td></td>
<td>Dr Helen Barker MDT Lead Clinician</td>
<td>Dr J Wright</td>
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<td>Dr H Barker</td>
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<td>Dr N Morley</td>
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<td>SY Region Haematology MDT</td>
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<tr>
<td>The Sheffield Teaching Hospitals NHS Foundation Trust (STHFT), Barnsley Hospital NHS Foundation Trust (BHNFT), Chesterfield Royal Hospital NHS Foundation Trust (CRHFT), Doncaster and Bassetlaw Hospitals NHS Foundation Trust (DBHNFT) and The Rotherham NHS Foundation Trust (TRFT)</td>
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<td></td>
<td>May 2017</td>
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**For more information on this document please contact:-**

Insert names of authors of the section:  Dr J Wright
Dr H Barker
Dr N Morley

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**Version History**

<table>
<thead>
<tr>
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<th>Brief Summary of amendments</th>
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<td>2</td>
<td>February 2016</td>
<td>Hodgkin Lymphoma updated</td>
<td>Dr J Wright</td>
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<tr>
<td>3</td>
<td>May 2016</td>
<td>Diffuse Large B Cell Lymphoma updated</td>
<td>Dr J Wright</td>
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*(Please note that if there is insufficient space on this page to show all versions, it is only necessary to show the previous 2 versions)*

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LYMPHOPROLIFERATIVE DIAGNOSTIC GUIDELINES

All samples from patients with suspected lymphoma should be assessed by the Haemato-oncology Diagnostic Service based at the Hallamshire Hospital, Sheffield Teaching Hospitals, NHS Trust. (STH)

VIROLOGICAL TESING IN LYMPHOMA:
The implications of HIV to patients with lymphoma are significant. DLBCL, Burkitt lymphoma and Primary effusion lymphoma are those most commonly associated with HIV but with the exception of follicular and mantle cell lymphomas associations with all other subtypes have been reported. Hepatitis C has been reported in association with a variety of lymphoma subtypes. Hepatitis B maybe reactivated in rituximab containing regimes.

To avoid omissions it is therefore advised that all new patients are tested for HIV, hepatitis B (SAg and core antibody) and C

Tissue Diagnosis of Lymphoproliferative Diseases

These arrangements apply to all cases of lymphoma and related haematological tumours with the exception of primary cutaneous T-cell lymphomas, which will be managed through the skin tumour MDT.

Local Diagnosis:
Network referral Hospitals and all STH non-HODS histopathologists:

Most patients will have their diagnosis suspected by non-specialist histopathologists. Fixed tissue will be submitted for paraffin sections. This should apply to nodal and extranodal lymphoma.

The non-HODS histopathologists should investigate the biopsy as locally agreed before referral to the HODS-Haematopathology team at STH. All relevant tissue blocks and all stained slides should be sent as soon as possible with a completed HODS referral form. If it is considered useful to retain something at the source laboratory, then a duplicate H&E section is suggested.

In some instances, whilst H&E staining will be sufficient, in others immunohistochemical (IHC) investigation of an “undifferentiated tumour” will detect a lymphoma. The initial IHC panel recommended for a suspected Non-Hodgkin lymphoma diagnosis is CD3, CD20, CD30 and Ki67. Further investigation is not recommended without conferring with the HODS-histopathology team, to ensure maximum tissue conservation.

Please contact the HODS histopathology team if there is any urgency for the report.

HODS-Histopathology lymphoma Diagnoses

Investigation will be carried out in the manner of the guidance Best Practice in Lymphoma Diagnosis and Reporting issued by the BCSH.RCPath, 2008 and its Appendix 1, which lists the criteria for diagnosis of each entity. The diagnoses will be according to the latest WHO classification category whenever possible, and to a level of clinical utility in other circumstances. Some cases may have ancillary investigations thought to be of diagnostic and prognostic significance.

H&E histological evaluation will guide the differential diagnosis and the choice of markers.
Cases will be investigated sequentially with selected panels of markers depending on prior investigations. Shortage of material may result in omitting some markers. Flow cytometry will not be routinely used for solid tissue diagnosis for the time being.

Cytogenetic testing using FISH will be requested when needed (and sometimes after discussion with the clinician) from the Sheffield Diagnostic Genetics Service at the Sheffield Children’s Hospital. PCR testing for immunoglobulin and/or T-cell receptor clonality will be done at

References


Bone Marrow Trephine Biopsy HODS Examination

Though investigated somewhat separately from its corresponding aspirate sample, the choice of investigation protocols and interpretation will be influenced by the aspirate findings, and the final report will be integrated with the current information from all investigation modalities. Hence on many occasions the trephine biopsy investigations will be curtailed if they would not add to the total information content of the integrated report. The choice of tests will also be influenced by findings uncovered during the course of investigation.

The particular focus of this guidance is the use of standard immunohistochemistry panels, tailored to the clinical context of the trephine biopsy. It does not seek to be an exhaustive list of all possible scenarios, and those not listed will be investigated according to professional judgement.

Clinical and Pathological Scenarios

Initial staging of known lymphoma

- HD: not routine immuno
- B NHL: not routine
  - If required CD3, CD20
- T NHL: routine CD3, CD20, CD4, CD8, CD30

Reporting involvement in staging marrows

- None seen
  - ... “without evidence of lymphoma”
- Lymphoma present; describe quantity
  - Light / moderate / heavy disease load or percentage of marrow colonised
  - Compare with known lymphoma and state if similar or discrepant
  - Compare with previous bone marrows if relevant

Bone marrow lymphocytosis

- Check history and other investigations
- If still in doubt
  - CD3, CD20 then decide which panels

BMT for investigation of fever or other B-symptoms

- Routine CD3, CD20, CD30

Investigation of neutropenia

- Unless obvious cause, CD3, CD20, CD4, CD8 (seeking LGL infiltrate)

First diagnosis of lymphoma from BMT

Usual lymph node panels and sequence but with a lower threshold for including cytokeratin and S100

Acute leukaemia

- Not routine immunos, if satisfactory aspirate or peripheral blood results
- TdT, CD3, CD20, CD10, CD15, CD43, CD79a, myeloperoxidase
- Reticulin stain will be done
Investigation of serum immunoglobulin monoclonal, ?MGUS, Diagnosis or follow-up of plasma cell myeloma

- Routine immunos CD138 and MUM1
- Give estimate of plasma cell % of nucleated cells

Investigation of ?myelodysplasia

- Not routine immunos
- Routine reticulin stain
  - For problematic cases and hypoplastic marrow
    - Glycophorin, myeloperoxidase, CD34, CD61

Investigation of ?myeloproliferative disorder

- Not routine immunos, sometimes as below
- Routine reticulin stain
- CML / CMML
  - Myeloperoxidase, CD68(PGM1 and KP1), CD34, CD117
- Myelofibrosis
  - CD61 and other stains to account for non-haematological fibrosis according to morphology.
Chlorambucil Oral Chemotherapy Regimen for Follicular Lymphoma

- accept that Chlorambucil is palliative ∴ CR unnecessary
- aim for control of symptoms and best tumour response
- a sensible regimen is:

|-------------|------|------|------|------|------|------|------|------|------|------|

optional
Recommendation for all appropriate Lymphoma Regimes:

Echocardiograms should be performed on patients being considered for anthracycline treatment if they are aged over 70 years, or if they have a history of cardiovascular problems.

Use of Rituximab
The evidence for the use of Rituximab at present is firm in that it is currently recommended first line for cases of Follicular Lymphoma and DLBCL only. However, it is recommended that Rituximab should also be requested for use in the following two instances:

i. Patients who have failed Chlorambucil or COP for Follicular Lymphoma should be given Rituximab.
ii. Patients who have been treated with R-CVP should continue with Rituximab maintenance for a set period.

Lymphoma Chemotherapy and Fertility

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Azoospermia</th>
<th>Persistent amenorrhoea</th>
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</thead>
<tbody>
<tr>
<td>ChIVPP/MOPP</td>
<td>&gt;80%</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>ABVD</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>BEACOPP</td>
<td>&gt;90%</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Stanford V</td>
<td>&gt;40%</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>CHOP (or CHOP-like)</td>
<td>&lt;30%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>ESHAP</td>
<td>&gt;80%</td>
<td>&gt;40%</td>
</tr>
<tr>
<td>IVE</td>
<td>&gt;80%</td>
<td>&gt;40%</td>
</tr>
<tr>
<td>High Dose</td>
<td>&gt;90%</td>
<td>&gt;80%</td>
</tr>
</tbody>
</table>
Classical Hodgkin Lymphoma

**Diagnosis**
All patients should have their diagnoses confirmed by HODS.

**Initial Staging**
Routine staging includes a CT scan of the neck, chest, abdomen and pelvis and a pre-treatment PET scan. Blood tests should include FBC, ESR, U/E’s, LFT’s and LDH. Viral screening should be performed for HIV, Hepatitis B and Hepatitis C. Bone marrow biopsy is not mandatory in all cases especially where the FBC is normal but should certainly be considered in advanced stage disease or where the FBC is abnormal. Consideration should be given to pre treatment ECHO and PFT’s in patients who have significant cardiac or respiratory problems.
The prognostic index for Hodgkin Lymphoma is the Hasenclever score which should be calculated for all patients (Adverse features = Male sex, Ann Arbor Stage 4, Age>45yrs, Albumin <40, Hb<105, Lymphopaenia<0.6 and total WCC>16).

**Treatment**
All cases should be discussed at the weekly MDT ideally prior to commencing treatment. Ideally patients should be treated in a clinical trial and should be offered transfer to another centre if a clinical trial is available there. Patients receiving Bleomycin should be assessed carefully for features of pulmonary toxicity

**Early Stage Disease**
Results from the RAPID study demonstrate a good outcome for patients achieving PET negativity (Deauville < 3), even without involved field radiotherapy.

Patients with Stage I-IIA Hodgkin Lymphoma above the diaphragm with no bulk mediastinal disease should undergo PET on Day 9-13 ABVD Cycle 3b.

REQUEST SHOULD MARKED AS URGENT WITH THE COMMENT:-
“INTERIM SCAN WITHIN 2 WEEKS OF COMPLETION OF CHEMOTHERAPY”
If negative (Deauville 1-2) then no further treatment is required, Those with positive scans (Deauville 3-5) should receive a 4th cycle of ABVD followed by IFRT.

**Advanced Stage Disease (Ann Arbor stages IIb–IV, or IIA with bulk or ≥3 involved sites)**
Data from the RATHL study confirm that around 75% of patients achieve PET negativity (Deauville 1-3) after 2 cycles. Such patients have excellent outcomes and evidence suggests bleomycin can be omitted from the remaining 4 cycles, reducing toxicity and late effects. Those achieving PET negativity after 2 cycles of ABVD should then receive a further 4 cycles of AVD. End of treatment IFRT is not required. Note if the interim PET scan result is not available before ABVD cycle 3a then continue with ABVD until the result becomes available. Do not interrupt or delay chemotherapy waiting for a PET scan result.

Patients should undergo repeat PET scanning Day 9-13 after ABVD Cycle 2b.

REQUEST SHOULD MARKED AS URGENT WITH THE COMMENT:-
“INTERIM SCAN WITHIN 2 WEEKS OF COMPLETION OF CHEMOTHERAPY”
Those patients not achieving PET negativity after 2 cycles should complete 6 cycles of ABVD followed by a further PET and discussion about the role of IFRT where applicable.

**Elderly patients**
Should be assessed for their fitness to receive combination chemotherapy.
Intensive treatment options include ABVD and VEPEMB.
Palliative options include VEDex and local radiotherapy.
Relapse

Patients who remain PET positive on completion of therapy should have a repeat biopsy or be followed up closely to look for early progression. A positive PET on its own is not sufficient evidence to proceed with salvage chemotherapy and autologous stem cell transplantation. Patients considered fit should be treated with 2-3 cycles of ESHAP, DHAP or IVE salvage chemotherapy. Where this leads to PET negativity it should be followed by an autologous stem cell transplant with BEAM conditioning. Patients remaining PET positive should be considered for a second salvage regimen in attempt to attain PET negativity prior to transplant.

Those relapsing following autologous stem cell transplantation may receive Brentuximab (CDF funding application required) with consideration given to allogeneic transplantation.

Those not considered fit for this approach may be treated with one of a number of palliative regimens including local radiotherapy, ChlVPP, VEDex or Gemcitabine and Oxaliplatin. Brentuximab is also funded by the CDF for treatment of relapsed or refractory Hodgkin lymphoma in patients who have failed at least two prior multi-agent chemotherapy regimens and are not ASCT candidates.

Follow up

Routine scanning or repeated CXR’s are not required. Consideration should be given to referral to the Late Effects Clinic especially in those treated at a young age or who have had more than one line of therapy.

Summary of Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD/AVD</td>
<td>First line curative</td>
</tr>
<tr>
<td>VEPEMB</td>
<td>First line curative</td>
</tr>
<tr>
<td>DHAP</td>
<td>Second line curative</td>
</tr>
<tr>
<td>ESHAP</td>
<td>Second line curative</td>
</tr>
<tr>
<td>IVE</td>
<td>Third line curative</td>
</tr>
<tr>
<td>Gemcitabine and Oxaliplatin</td>
<td>Second and subsequent line palliative</td>
</tr>
<tr>
<td>VEDex</td>
<td>First and subsequent line palliative</td>
</tr>
<tr>
<td>ChlVPP</td>
<td>Second and subsequent line palliative</td>
</tr>
<tr>
<td>Brentuximab</td>
<td>Following autologous stem cell transpl</td>
</tr>
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</table>
Nodular Lymphocyte Predominant Hodgkin Lymphoma

**Diagnosis**

All patients should have their diagnoses confirmed by HODS.

**Initial Staging**

Routine staging includes a CT scan of the neck, chest, abdomen and pelvis and a PET scan. Blood tests should include FBC, U/E’s, LFT’s and LDH. Viral screening should be performed for HIV, Hepatitis B and Hepatitis C. A bone marrow biopsy need not always be performed.

**Initial Treatment**

**Stage IA or IIA**

Following complete resection no treatment is necessary. Patients with incomplete resection should receive involved field radiotherapy.

**Advanced NLPHL**

This is rare at presentation. Treatment is controversial. Patients may be observed if well or treated with ABVD or R-CHOP.

**Relapse**

Re-biopsy is essential as patients may transform to DLBCL. Localised relapse may be treated with radiotherapy. Patients with generalised relapse should be treated as for DLBCL with R-CHOP. Subsequent relapses may require salvage treatment with ESHAP or DHAP and consolidated with a BEAM PBSCT.

**Summary of Regimens**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Indication</th>
</tr>
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<tbody>
<tr>
<td>ABVD</td>
<td>First or second line advanced stage</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>First or second line advanced stage</td>
</tr>
<tr>
<td>ESHAP</td>
<td>Second or subsequent line</td>
</tr>
<tr>
<td>DHAP</td>
<td>Second or subsequent line</td>
</tr>
<tr>
<td>BEAM</td>
<td>Second or subsequent line</td>
</tr>
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</table>
Management of Extranodal Marginal Zone Lymphoma of mucosa associated lymphoid tissue

Investigations

- FBC, ESR, LDH, renal and liver functions, Serum Immunoglobulins and electrophoresis, Hepatitis B, C and HIV serology
- Bone marrow aspiration and trephine biopsy
- CT scan of chest, abdomen, pelvis
- PET scan not necessary

Treatment

Gastric MALToma:

Stage 1E- Eradication treatment for Helicobacter Pylori, even if test for Helicobacter is negative
Follow-up gastroscopy 6 monthly for 2 years

Recurrent or persistent disease can be treated with further H Pylori eradication treatment.

Patients with recurrent or persistent histological disease and macroscopically normal stomach does not require treatment.

Stage greater than 1E, symptomatic disease and bulky disease can be treated with R-Chlorambucil.

Other treatment options for bulky disease include R-Bendamustine (CDF), R-CVP, R-Fludarabine and R-CHOP.

Symptomatic disease persisting after 6 courses of R-chlorambucil can be treated with a purine analogue.

Surgery is required only for perforation or for uncontrolled bleeding.

Radiotherapy is generally not required for gastric MALToma.

Extra nodal marginal zone lymphoma at other sites:

Stage 1E- can be treated with local radiotherapy with curative intent.
Advanced stage disease in asymptomatic patients- Watch and wait approach is reasonable.

Bulky or symptomatic disease- Treatment options include R-Bendamustine, R-CVP, R-CHOP and R-Fludarabine.
Local radiotherapy can be offered for bulky symptomatic disease.

Transformation to DLBL- should be treated just as for de novo DLBL
Diffuse Large B cell Lymphoma (DLBCL)

1. Diagnostic Criteria

All patients should have their diagnoses confirmed by HODS.

Table 1: DLBCL: variants, subgroups and subtypes/entities

<table>
<thead>
<tr>
<th>Diffuse large B-cell lymphoma (NOS)</th>
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<tr>
<td>Common morphologic variants – centroblastic, immunoblastic and anaplastic</td>
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<tr>
<td>Rare morphologic variants</td>
</tr>
<tr>
<td>Molecular Subgroups – Germinal centre B-cell like, Activated B-cell like</td>
</tr>
<tr>
<td>Immunohistochemical subgroups – CD5-positive DLBCL, Germinal centre B-cell like, Non-germinal centre B-cell like</td>
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<thead>
<tr>
<th>Diffuse large B-cell lymphoma subtypes</th>
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<tbody>
<tr>
<td>T-cell/ histiocyte-rich large B-cell lymphoma</td>
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<tr>
<td>Primary DLBCL of the CNS</td>
</tr>
<tr>
<td>Primary cutaneous DLBCL, leg type</td>
</tr>
<tr>
<td>EBV positive DLBCL of the elderly</td>
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<tr>
<th>Other lymphomas of large B cells</th>
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<tbody>
<tr>
<td>Primary mediastinal (thymic) large B-cell lymphoma</td>
</tr>
<tr>
<td>Intravascular large B-cell lymphoma</td>
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<tr>
<td>DLBCL associated with chronic inflammation</td>
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<tr>
<td>Lymphomatoid granulomatosis</td>
</tr>
<tr>
<td>ALK-positive large B-cell lymphoma</td>
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<tr>
<td>Plasmablastic lymphoma</td>
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<tr>
<td>Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
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<th>Borderline cases</th>
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<tbody>
<tr>
<td>B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma</td>
</tr>
<tr>
<td>B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma</td>
</tr>
</tbody>
</table>

2. Recommended Staging Investigations

Blood tests
FBC
U/E’s, LFT’s, Ca, LDH, serum urate, serum immunoglobulins.
Viral serology for HIV, Hepatitis B and C

Bone marrow biopsy.

Imaging
CT scan of thorax, abdomen and pelvis (and neck if clinically involved).
Those with disease primarily affecting the CNS or Head and Neck region an MRI should be performed. PET-CT is recommended as a staging investigation. WHO/ECOG performance status. Calculation of International Prognostic Index (IPI). Assessment of cardiac function by echocardiography should be considered in elderly patients and those with a history of cardiac disease.

3. Primary Treatment

Non-bulky Stage IA
R-CHOP x 3 plus involved field radiotherapy.

All other patients
Patients with both nodal and extranodal presentations should be treated with 6-8 x CHOP & Rituximab (at physicians discretion). All patients should be considered for REMoDL-B trial.

In frail patients consideration may be given to the use of R-PMitCEBO as an alternative to R-CHOP. In those with a poor PS/ significant co-morbidity, VEDex may be given as palliation.

Radiotherapy may be considered for patients with persistent PET positivity at the end of treatment or those with localised bulky disease at presentation. Any cases where the role of consolidation radiotherapy is under consideration should be discussed in the weekly radiology section of the Regional MDT meeting.

High-risk patients
Patients with high risk disease e.g. “double hit” lymphomas, suspected/confirmed CNS disease at presentation or high IPI cases in younger patients may be considered for R-CODOX-M/R-IVAC. Such cases should be discussed urgently at the MDT/review meeting.

Other considerations
- Patients with extensive tumour, high LDH and urate may be at risk of tumour lysis. Consideration should be given to the use of Rasburicase.
- In some cases of primary extranodal DLBCL radiotherapy is indicated following systemic treatment (Reyes, Lepage et al. 2005) i.e. testicular Lymphoma: contra lateral testis and primary lymphoma of bone.
- Patients with immunsupression related lymphoma e.g. PTLD or HIV-related lymphoma should be discussed at the MDT and referred to Sheffield as they are often difficult cases requiring input from multiple specialities.
- Because of the high rate of CNS relapse patients with testicular involvement should receive a regime of RCHOP alternating with high dose methotrexate (3.5g/m2) after courses 2 and 4.

4. CNS prophylaxis for presenting patients with Diffuse Large B-cell Lymphoma

The role of CNS involvement prophylaxis is controversial and data is lacking. The incidence of CNS relapsed has reduced since the introduction of rituximab.

The optimum approach to CNS prophylaxis is uncertain. Strategies for the identification of individuals at risk of CNS relapse are flawed.
With the exception of testicular lymphoma, and on the basis of current data, CNS prophylaxis is not routinely offered (outside clinical trials) within North Trent.

5. Relapsed DLBCL

Where possible all patients with symptoms or signs suggestive of relapsing disease should undergo a further biopsy.
For those who are fit enough, the strategy should be to induce remission and consolidate using a BEAM autograft.

Patients who are fit enough should receive R-ESHAP/ R-DHAP or R-IVE followed by a BEAM autograft in responding patients.
Patients not considered candidates for autologous transplantation should be treated palliatively.
Suitable regimens include ESHAP, PMitCEBO, VEDex or Pixantrone (NICE TA306). The outcome of chemotherapy without a high dose procedure is poor.
Radiotherapy has a role in limited stage relapse where autograft is not an option or as palliative therapy.
There is some evidence that gemcitabine/oxiplatin combinations maybe of benefit as third line chemotherapy in those patients not responding to a standard approach. In some cases this may allow autografting to be reconsidered (Lopez et al 2008).

For those cases relapsing following an autograft the prognosis is very poor. For those who are younger and fitter an allogeneic transplant may be considered. Such cases should be discussed at the MDT.

6. Assessment post chemotherapy

- Patients should undergo PET/ CT scanning post treatment.
- PET maybe useful for the assessment of any residual masses and to inform decisions regarding consolidation radiotherapy.
- Where there is uncertainty about interpretation of EOT PET regional haematologists are encouraged to refer cases for discussion at the Monday lymphoma meetings.
- A programme of regular scans following completion of treatment is not recommended. Scans are indicated only for physician or warranted patient concern.
- In the relapsed disease setting PET scanning should be performed to assess response pre BEAM autograft. Patients who are PET negative pre BEAM have an improved outcome.
- Bone marrow examination should be repeated in those with marrow involvement at presentation.

7. Summary of chemotherapy regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP</td>
<td>First line (additional Methotrexate 3.5g/m2 x2 for testicular lymphoma)</td>
</tr>
<tr>
<td>R-PMitCEBO</td>
<td>First line elderly/frail</td>
</tr>
<tr>
<td>R-CODOX-M/R-IVAC</td>
<td>First line high risk</td>
</tr>
<tr>
<td>R-ESHAP /DHAP</td>
<td>Second or subsequent line</td>
</tr>
<tr>
<td>IVE</td>
<td>Third line</td>
</tr>
<tr>
<td>GemOx</td>
<td>Third or subsequent line</td>
</tr>
<tr>
<td>VEDex</td>
<td>First and subsequent line palliative</td>
</tr>
<tr>
<td>Pixantrone</td>
<td>Third or subsequent line</td>
</tr>
</tbody>
</table>
Burkitt Lymphoma

**Key issues**

- CODOX-M/IVAC plus rituximab remains the best available treatment
- Recent data on infusional chemotherapy regimes shows other approaches may be useful but data inadequate at present (Dunleavey et al 2013, NEJM)
- Continuing problems with diagnostic criteria.
- Better therapies are required for elderly patients with Burkitts

**Diagnostic Criteria**

All patients should have their diagnoses confirmed by HODS.

**Essential Investigations**

- As for Diffuse Large B-cell lymphoma *plus* examination of the CNS (CSF and CT head) in all cases.
  - MRI brain may also be required if there is a suspicion of CNS involvement.

**Primary Treatment**

- R CODOX-M/ R IVAC.
- There are considerable issues regarding initial treatment toxicity and tumour lysis – Rasburicase pre-treatment should be considered especially in patients with high bulk and/or abnormal renal function.

**Relapsed disease**

There is no consensus or trial. Outcome would be expected to be very poor. There is little evidence base for intensification of therapy and cases should be carefully reviewed in the relevant MDT.
Lymphoblastic Lymphoma (B & T cell)
Such cases should be regarded as ALL and managed in the same way. Please see ALL section.
Follicular Lymphoma

**Essential Investigations**

- The International Prognostic Index modified for follicular lymphoma (FLIPI) should be calculated for all patients (Kondo, Ogura et al. 2001; Montoto, Lopez-Guillermo et al. 2002). B2 microglobulin is also of strong prognostic significance.
- CT scan of thorax, abdomen, pelvis (and neck if clinically involved). Although the majority of follicular lymphomas are PET avid this imaging modality is not routinely indicated.
- Bone marrow biopsy
- HIV, hep B and C

**Primary Treatment**

**Stage IA**

Patients with stage 1A or 2A where the disease site can be included in one radiation field should be referred for local radiotherapy with curative intent.

It is not necessary to do PET scan to confirm early stage of the disease before referring patients for radiotherapy.

**All other patients**

- Active monitoring / watch and wait in asymptomatic patients.
- Rituximab containing regimen eg.6 courses of R-CVP for the majority of patients to be followed by rituximab maintenance 2 monthly for 2 years
- Older patients unfit for R-CVP chemotherapy can be considered for R- Chlorambucil
- (NICE guidance) or R- Bendamustine (notify CDF)
- There is no role for upfront autograft or allograft in follicular lymphoma
- Histological grade 3B should be treated as DLBL with CHOP-R

**Transformed Follicular Lymphoma**

In 25-35% of patients with FL, transformation or ‘progression’ to a high grade lymphoma occurs. This is usually a DLBCL, but occasionally it resembles Burkitt Lymphoma or with features intermediate between DCBCL and Burkitt lymphoma. This is usually associated with rapid progressive clinical course and death from tumour refractory to treatment. Rarely, patients develop acute B-cell lymphoblastic leukaemia.

This group includes patients presenting in transformation and those relapsing with transformed disease.

- Investigate and treat as for DLBCL
- CHOP-Rituximab should be given as primary therapy
- Those who have previously received CHOP should be treated as for a relapsed DLBCL
- There is some evidence that autograft may be of benefit and cases should be discussed at the regional MDT and/or Lymphoma review meeting.
Relapsed Follicular NHL

Repeat biopsy should be undertaken wherever possible to re-confirm the diagnosis prior to further treatment.

Relapsed patients should receive R chemotherapy (eg R- CVP for late relapse, R-CHOP for early relapse after R-CVP) followed by 3-monthly R-maintenance for 2 years.

Patients with relapsed or refractory follicular lymphoma who cannot tolerate CHOP-R or CVP-R are eligible to receive R-Bendamustine( notify CDF)

Patients who have received R for upfront treatment and R maintenance should still receive R-chemotherapy.

Patients who have received upfront R maintenance may not be suitable for further maintenance R after chemotherapy

Patients with relapsed follicular lymphoma who are unfit for chemotherapy can be considered for R monotherapy, weekly for 4 weeks

Patients relapsing early especially within 12 months should be considered for autograft.

Younger, fit patients with a suitable donor can be considered for miniallograft- discuss at North Trent MDT

Palliative radiotherapy is a useful treatment option for patients with localised symptomatic disease or if unfit for chemotherapy.

1 Other extranodal FL: FL can occur in almost any extranodal site and have similar morphology, immunophenotype and genetics to nodal FL. Patients usually have localised extranodal disease and systemic relapses are uncommon.

2 Intrafollicular neoplasia/ 'in situ' follicular lymphoma: This is a pathological diagnosis with uncertain clinical significance except that evaluation for overt FL elsewhere is needed.

Transformation

In 25-35% of patients with FL, transformation or 'progression' to a high grade lymphoma occurs. This is usually a DLBCL, but occasionally it resembles Burkitt Lymphoma or with features intermediate between DCBCL and Burkitt lymphoma. This is usually associated with rapid progressive clinical course and death from tumour refractory to treatment. Rarely, patients develop acute B-cell lymphoblastic leukaemia.

Essential Investigations

- The International Prognostic Index modified for follicular lymphoma (FLIPI) should be calculated for all patients (Kondo, Ogura et al. 2001; Montoto, Lopez-Guillermo et al. 2002). B2 microglobulin is also of strong prognostic significance.
- CT scan of thorax, abdomen, pelvis (and neck if clinically involved). Although the majority of follicular lymphomas are PET avid this imaging modality is not routinely indicated.
- Bone marrow biopsy
- HIV, hep B and C
**Primary Treatment**

**Stage IA**

Although there is relatively little data there is some evidence that patients with stage 1A may be curable. All patients should be referred for radiotherapy.

**All other patients**

- active monitoring / watch and wait in asymptomatic patients.
- Rituximab maintenance is pending NICE approval but currently funded through the Interim Cancer Drugs fund.

**Large cell variant +/- t(14;18)**

- Investigate and treat as for DLBCL (WHO 3B)

**Transformed Follicular Lymphoma**

This group includes patients presenting in transformation and those relapsing with transformed disease.

- Investigate and treat as for DLBCL
- CHOP-Rituximab should be given as primary therapy
- Those who have previously received CHOP should be treated as for a relapsed DLBCL
- There is some evidence that autograft may be of benefit and cases should be discussed at the regional MDT and/or Lymphoma review meeting.

**Relapsed Follicular NHL**

Repeat biopsy should be undertaken wherever possible to re-confirm the diagnosis prior to further treatment.

Non trial patients should receive R chemotherapy followed R maintenance. Patients relapsing within 12 months and not eligible for SCHRIFT should be considered for autograft.

Palliative radiotherapy (including the FORT trial comparing standard dose palliative irradiation with low dose) is a useful treatment option for patients with localised symptomatic disease or if unfit for chemotherapy.

Certain patients may be considered for BEAM autograft or reduced intensity allograft and should be discussed at the North Trent MDT.
Mantle Cell Lymphoma

Recommended Initial Investigations

FBC, U/E’s, LFT’s, Ca\(^2\)+, LDH.
HepBsAg, HepBcAb, Hep C and HIV serology.
Bone marrow aspirate and trephine biopsy.
CT scan of chest, abdomen and pelvis. Include neck if clinically involved.
Consider GI investigations if involvement is clinically suspected.
PET scan is not routinely recommended in mantle cell lymphoma.

Recommend enter into MCL Biobank Study which is open in Sheffield.

Initial Treatment

Stage 1A disease- Refer for involved field radiotherapy.

Higher stage, asymptomatic disease- wait and watch.

Higher stage, symptomatic disease

   Less than 65 years, fit for PBSCT,
       R-CHOP alternating with R-DHAP (or R-ESHAP) followed by PBSCT.

   Over 65 or below 65 and not fit for PBSCT:
       VR-CAP (NICE Approved)
       R- Bendamustine
       R-CVP
       R-CHOP
       R-FC

   Older, frail patients: Single agent oral Chlorambucil or R-Chlorambucil.

   Patients may also receive maintenance rituximab.

Management of relapsed MCL

Fit patients who haven’t had upfront PBSCT- consider R-CHOP (if they haven’t had CHOP before) followed by PBSCT.

Younger, fit patients with relapsed disease and a matched donor should be considered for a reduced intensity allograft.

Less fit patients can be treated with CVP-R, FC-R, R- bendamustine ( CDF), R-chlorambucil

Multiply relapsed patients can be considered for bortezomib or lenalidomide but funding has to be secured before starting treatment.

Ibrutinib as per CDF conditions.
## Summary of treatment regimens for MCL

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral chlorambucil</td>
<td>First and subsequent line, palliative</td>
</tr>
<tr>
<td>R-Chlorambucil</td>
<td>First and subsequent line, palliative</td>
</tr>
<tr>
<td>R-CVP</td>
<td>First and subsequent line</td>
</tr>
<tr>
<td>R-PMitCEBO</td>
<td>First and subsequent line</td>
</tr>
<tr>
<td>R-FC</td>
<td>First and subsequent line</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>First and subsequent line</td>
</tr>
<tr>
<td>R-Bendamustine**</td>
<td>First and subsequent line (as per CDF guidelines)</td>
</tr>
<tr>
<td>VR-CAP</td>
<td>First line not fit for transplant</td>
</tr>
<tr>
<td>R-CHOP/R-DHAP</td>
<td>First line fit&lt;65yrs</td>
</tr>
<tr>
<td>BEAM</td>
<td>Autologous transplant conditioning</td>
</tr>
<tr>
<td>VEDex</td>
<td>Second and subsequent line, palliative</td>
</tr>
<tr>
<td>ESHAP</td>
<td>Second and subsequent line, intensive</td>
</tr>
<tr>
<td>Ibrutinib**</td>
<td>Second and subsequent line</td>
</tr>
<tr>
<td>Velcade**</td>
<td>Third and subsequent line</td>
</tr>
<tr>
<td>Lenalidomide**</td>
<td>Third and subsequent line</td>
</tr>
</tbody>
</table>

** indicates funding required usually through CDF
T Cell Lymphomas

This guidance is for patients with systemic lymphomas and not for those with primary cutaneous T-cell lymphoma. These cases should be discussed at the MDT in the Dermatology Section before treatment is initiated.
For more detailed guidance see BCSH Guidelines updated August 2013.

**Diagnosis**

All cases should have their diagnosis confirmed by HODS.

**Initial Staging**

Routine staging includes a CT scan of the neck, chest, abdomen and pelvis.
PET scanning is not routinely required.
Blood tests should include FBC, ESR, U/E’s, LFT’s and LDH.
Viral screening should be performed for HIV, Hepatitis B, Hepatitis C and HTLV I+II.
A bone marrow biopsy should be performed.

**Initial Treatment**

Entry into a clinical trial should be considered where possible.
Current front line study open in Sheffield is Chemo T comparing GEMP to CHOP for Peripheral T-cell lymphoma NOS, systemic ALK negative ALCL, AITL and Hepatosplenic T-cell lymphoma.

- **Anaplastic large cell lymphoma**
  standard treatment is with 6-8# CHOP.

- **Peripheral T cell lymphoma NOS**
  standard treatment is with 6-8# CHOP.

- **Angio-immunoblastic lymphoma**
  standard treatment is with 6-8# CHOP.
  continuous low dose prednisolone/cyclophosphamide has a role in those not fit for this.

- **Hepatosplenic T-cell lymphoma**
  no standard treatment. Discuss individual cases.

- **Enteropathy associated T-cell lymphoma**
  fit patients should receive IVE/Methotrexate followed by BEAM ASCT transplant (as per ITCL study).

- **Extranodal NK/T cell lymphoma, nasal type**
  responses to CHOP are limited consider radiotherapy for localised disease or Asparaginase based treatment (e.g. SMILE) for more widespread disease.

- **T-Large Granular Lymphocytic Leukaemia**
  asymptomatic patients should be observed.
  Symptomatic disease try oral low dose methotrexate.
  Oral cyclosporin may also be used in patients.
  Oral steroids and growth factor support may produce short term improvement.
Relapse

Patients with relapsed disease present even more of a challenge and should be discussed at the MDT prior to commencing therapy.
MANAGEMENT OF Chronic Lymphocytic Leukaemia (CLL)

This is a chronic leukaemia of CD5+ B-cells. The term includes cases presenting with lymphadenopathy, known as small lymphocytic lymphoma. Patients may present with lymphadenopathy, systemic symptoms such as tiredness, night sweats and weight loss or the symptoms of anaemia or infection. However, 70–80% of patients are now diagnosed as an incidental finding on a routine full blood count.

The IWCLL and WHO Guidelines define CLL as involvement of bone marrow and blood with the presence of a persistent monoclonal B lymphocytosis >5x10⁹/l marking as CLL. The diagnosis may also be made with lower lymphocyte counts in patients with extramedullary involvement, cytopaenias or disease related symptoms. Patients with B lymphocyte counts ≤ 5 may be labelled as monoclonal B lymphocytosis rather than CLL. Monoclonal B-lymphocytosis may progress to frank CLL at a rate of 1% to 2% per year.

However, it could be argued that diagnosing an Indolent Lymphoproliferative disorder at such an early stage is not in the patient's best interest, causing unnecessary anxiety and Hospital Attendance. This should be borne in mind when reporting routine blood films and in discussion with GP's. The local recommendation is that lymphocytosis of <10x10⁹/l should not be investigated unless there are other adverse features.

These treatment guidelines are based upon the BCSH CLL guidelines interim statement 2015 (www.bcshguidelines.com).

1. Diagnosis

All patients should have their diagnoses confirmed by HODS.

2. Investigations

Other investigations which may be helpful at time of diagnosis or during course of disease:-

Direct Antiglobulin Test
Reticulocyte Count
Serum Immunoglobulins
CT scan may be helpful in bulky lymphadenopathy to help monitor response

Bone marrow aspiration and Trephine - Although marrow examination is not usually essential for the diagnosis support a diagnosis of CLL in cases with atypical morphology and a low immunophenotype score it may be helpful to help distinguish from mantle cell lymphoma. Marrow examination is also valuable for determining the cause of cytopenias, providing prognostic information and assessing the response to therapy.

Lymph node biopsy is not required for diagnosis but may be indicated if diagnosis uncertain, or in patients who develop bulky lymphadenopathy to exclude transformation to lymphoma.

Assessment of p53 deletions by FISH:

This is not indicated in all patients with CLL, but should be performed in patients prior to initial and subsequent treatments. Patients with p53 deletions in >20% of cells by FISH are usually resistant to purine analogues and alkylating agents. And alternative treatment strategies are required..The 2015 BCSH interim guidelines for CLL advise first line treatment with B cell receptor (BCR) signalling pathway inhibitor such as Idelalisib or Ibrutinib. Alemtuzumab +/- steroids is an
alternative for patients considered fit enough. Because of the potentially poor prognosis of p53 deleted CLL, allogeneic transplantation may need to be considered although its positioning is changing as more data is collected about outcomes with first and second line treatment with BCR signalling pathway inhibitors.

The full Vysis FISH panel looking for 11q deletion, Trisomy 12, 13q deletion and 17p deletion is available but not routinely recommended.

Patients due to receive monoclonal antibody treatments should be screened for Hepatitis B, C and HIV

3. Staging

Patients should be staged according to the Rai and Binet systems. Secondary causes of anaemia must be identified and treated before staging.

<table>
<thead>
<tr>
<th>Binet Stage</th>
<th>Organ involvement</th>
<th>Hb g/l</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0-2 areas</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>B</td>
<td>3-5 areas</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>C</td>
<td>NA</td>
<td>&lt;100 and/or</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rai Stage</th>
<th>Risk Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
</tr>
<tr>
<td>1</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>II</td>
<td>Intermediate</td>
</tr>
<tr>
<td>III/IV</td>
<td>High</td>
</tr>
</tbody>
</table>

Lymphocytosis only
Hepatomegaly or splenomegaly
Haemoglobin <110g/l or Platelets <100

4. Indications for Treatment

According to the IWCLL Guidelines,

1. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia
2. Massive (i.e., at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly
3. Massive nodes (i.e., at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
4. Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months. In patients with initial blood lymphocyte counts of less than 30x10^9/L, LDT should not be used as a single parameter to define a treatment indication.
5. Autoimmune anaemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy.
6. Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:
   a. Unintentional weight loss of 10% or more within the previous 6 months;
   b. significant fatigue (i.e., ECOG PS 2 or worse; inability to work or perform usual activities);
   c. fevers higher than 100.5°F or 38.0°C for 2 or more weeks without other evidence of infection; or
   d. night sweats for more than 1 month without evidence of infection.
Hypogammaglobulinemia or monoclonal paraproteinemia does not by itself constitute a basis for initiating therapy. However, it is recommended to assess the change of these protein abnormalities if patients are treated. Patients with CLL may present with a markedly elevated lymphocyte count; however, the symptoms associated with hyperleukocytosis that develop in patients with acute leukaemia rarely occur in patients with CLL. Therefore, the absolute lymphocyte count should not be used as the sole indicator for treatment.

4. Initial Treatment

Asymptomatic patients

Treatment of early stage disease is not indicated.

Symptomatic patients

Treatment is broadly stratified according to the patient’s fitness for therapy and the loss of p53 function.

1st Line treatment, fit patients with no loss of p53

Patients up to the age of 75 can be offered treatment in the FLAIR trial randomising between Fludarabine, Cyclophosphamide and Rituximab versus Ibrutinib and Rituximab

Patients with good performance status non-trial, should receive oral Fludarabine, Cyclophosphamide and Rituximab, (NICE TA174). All patients receiving FCR should have assessment of creatinine clearance so that appropriate dose adjustments can be made. This is particularly important in older patients. Patients should receive irradiated blood products. Allopurinol should be prescribed with the first cycle of treatment. Fludarabine monotherapy is not recommended for first line therapy (NICE TA119)

The interim BCSH guidelines suggest Bendamustine and Rituximab for patients who are fit but where FCR is contraindicated or who are older or for patient preference. Bendamustine is approved according to NICE TA216

Fit patients with loss of p53

The 2015 BCSH interim guidelines for CLL advise first line treatment with B cell receptor (BCR) signalling pathway inhibitor such as Idelalisib and Rituximab (NICE approved) or Ibrutinib (application to Cancer Drug Fund required). Alemtuzumab +/- steroids is an alternative for patients considered fit enough. Because of the potentially poor prognosis of p53 deleted CLL, allogeneic transplantation may need to be considered although its positioning is changing as more data is collected about outcomes with first and second line treatment with BCR signalling pathway inhibitors.

1st Line treatment of less fit patients with no loss of p53

The RIALtO trial is available for elderly patients first line comparing ofatumumab and chlorambucil (O-Chl) versus ofatumumab and bendamustine (O-B) in patients with CLL who are considered not fit enough for rituximab, fludarabine and cyclophosphamide (R-FC).
Both Chlorambucil and Ofatumumab and Chlorambucil and Obinutuzumab are approved by NICE for first line treatment of less fit patients. Combination of chlorambucil with one of these anti CD20 monoclonal antibodies has improved progression free survival and duration of first remission.

1st Line treatment of less fit patients with loss of p53

B cell receptor signalling pathway inhibitors such as Ibrutinib or Idelalasib are suitable for the treatment of less fit patients with loss of p53. Funding application is required for ibrutinib. Idelalasib and Rituximab is NICE approved.

1st Line treatment of frail elderly

Single agent chlorambucil remains a suitable palliative option for patients too frail for risks of infection and infusion reactions associated with anti CD20 therapies or those who do not wish to receive infusional therapies.

Maintenance Therapy

Maintenance therapy in patients after 1st line chemo-immuno therapy is currently under investigation in clinical trials. Patients can be offered entry in to the GALACTIC trial randomising MRD positive patients to obinutuzumab versus observation.

5. Treatment of relapse

For bulky relapse consider repeat biopsy to look for high grade transformation.

Publication of the RESONATE study (Ibrutinib versus Ofatumumab in previously treated Chronic Lymphocytic Leukaemia) and Idelalasib with Rituximab in relapsed/refractory CLL has changed the treatment options for 2nd and subsequent lines of therapy for CLL. Funding for these treatment options is governed by specific criteria. Idelalasib and Rituximab is NICE approved (TA359). Ibrutinib is available by application to the Cancer Drug Fund. Individual patient factors need to be taken into account when considering choice of drug.

According to the BCSH 2015 interim guidelines for CLL, fit patients at relapse who do not meet the criteria for treatment with Ibrutinib or Idelalasib should receive chemotherapy +/- Rituximab usually Bendamustine and Rituximab or FCR.

Oral Chlorambucil is suitable for older or unfit patients and can be used for retreatment. Rituximab can be used in addition if patient considered fit enough.

CHOP or CHOP like therapies - anthracycline containing regimens are less effective than purine analogues in patients previously treated with chlorambucil, but do have activity in patients relapsing after purine analogue therapy.

High dose Methylprednisolone - can be useful in patients refractory to other forms of treatment.

Alemtuzumab given subcutaneously at a dose of 30 mg three times per week for 12 weeks may be effective for refractory disease or those relapsing after purine analogues. Alemtuzumab should be used in patients with bone marrow infiltration rather than those with bulk disease. Ten per cent of patients develop cytomegalovirus (CMV) reactivation therefore regular monitoring of CMV viral...
load is required during therapy. Use of irradiated blood products is recommended following Alemtuzumab. Duration of remission is likely to be short, referral for allogeneic transplantation in suitable patients should be considered. For patients not suitable for transplant relapsing more than 12 months after first course of alemtumab can be retreated with alemtuzumab.

6. Transplantation

Although intensive treatments are not appropriate for the majority of patients with CLL approximately 20% of patients are 55 years of age at diagnosis. It is reasonable to consider stem cell transplantation in patients of good performance status as an option in individual circumstances. Early discussion with the Transplant Centre is recommended. Where possible, patients should be entered into clinical trials.

Autografting is not recommended.

Allografting maybe a curative option but there is significant transplant related mortality and morbidity. Patients should be considered on a case by case basis.

7. Supportive Care

Infective complications account for up to 50% of all CLL deaths.

Antimicrobial prophylaxis should be considered for patients with hypogammaglobulinaemia and recurrent infection
Pneumocystis prophylaxis is recommended for patients requiring intensive or immunosuppressive treatment including first 6 months of treatment with Idelalasib.
Regular CMV monitoring and 2 weekly full blood counts are also recommended in first 6 months of treatment with Idelasib.
### 8. Summary of chemotherapy regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral chlorambucil</td>
<td>First and subsequent line less fit</td>
</tr>
<tr>
<td>FCR</td>
<td>First line intensive&lt;br&gt;Second and subsequent line (not previous received Rituximab)</td>
</tr>
<tr>
<td>Bendamustine+Rituximab</td>
<td>First line</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Line p53 deleted&lt;br&gt;Second and subsequent line</td>
</tr>
<tr>
<td>Idelalisib + Rituximab</td>
<td>Second and subsequent line</td>
</tr>
<tr>
<td>Fludarabine, Cyclophosphamide, Rituximab</td>
<td>Second and subsequent line</td>
</tr>
<tr>
<td>CHOP</td>
<td>Second and subsequent line</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>Second and subsequent line</td>
</tr>
<tr>
<td>R-Bendamustine</td>
<td>Second and subsequent line</td>
</tr>
<tr>
<td>High dose methylprednisolone</td>
<td>Third and subsequent line&lt;br&gt;P53 deleted CLL first and subsequent line</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Third and subsequent line&lt;br&gt;P53 deleted CLL first and subsequent line</td>
</tr>
<tr>
<td>FLAIR trial</td>
<td>Fit non p53 deleted first line</td>
</tr>
<tr>
<td>RIAltO trial</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line unfit for FCR</td>
</tr>
</tbody>
</table>
Guidelines for the Management of Hairy Cell Leukaemia

1 - Introduction

HCL is an uncommon B-cell lymphoproliferative disorder. The incidence has been estimated as 2% of all forms of leukaemia and 8% of mature B or T cell lymphoproliferative diseases. HCL affects middle-aged men more commonly than women; the male:female ratio is 4.5:1.

2 - Clinical and laboratory features

Patients may be asymptomatic presenting as an incidental finding. Symptomatic patients present with symptoms of cytopenia, commonly infection. Cytopenias usually affect two or three lineages, monocytopenia is a consistent feature. Total white counts tend to be low, usually less than 5 x 10^9/l and very rarely over 10 x 10^9/l, except in HCL-variant. Characteristic hairy cells are often seen in the peripheral blood. Splenomegaly is common.

3 - Diagnosis

Diagnosis must be confirmed by HODS. Peripheral blood and bone marrow aspirate and trephine are required.

4 - Staging and prognostic features

- There is no widely agreed system for staging HCL.
- Heavy bone marrow infiltration and a large spleen will result in maximum degrees of cytopenia. Anaemia (< 100g/l), neutropenia (< 1.0 x 10^9/l) and thrombocytopenia (< 100 x 10^9/l) in any combination has been associated with poor prognosis. However, the early studies were published before the era of effective treatments for this disease, and prognostic factors should now include response to therapy.
- CT scan at presentation is not considered essential but may provide some prognostic information. If lymphadenopathy has been demonstrated, response assessments should include a repeat CT.
- Patients presenting with bulky abdominal lymphadenopathy respond less well to first-line therapy as this manifestation may represent a degree of transformation of the disease.
- An assessment of prognostic factors should also include response to purine analogue therapy. Those achieving only a partial response (PR) fare significantly worse than patients achieving complete remission (CR)

5 - Treatment

- Rarely (< 1% of cases) the patient is asymptomatic and the cytopenias are minimal and watch and wait with active monitoring is appropriate.
- Patients with symptomatic cytopenia or painful splenomegaly require treatment. None of the treatment modalities have been tested in large randomised trials.
- Purine analogues cladribine is the usual agents first line. Pentostatin is also effective. Both agents induce a high rate (> 80%) of complete remissions which, in the majority of patients, are prolonged. Lifelong irradiated blood products are required following purine analogues.
- Partial response to purine analogues is now regarded as a poor prognostic factor. Bone marrow assessment after count recovery (typically 4-6 months after cladribine therapy or following 8-9 courses of pentostatin) is recommended. A second course of purine analogue therapy is recommended if patients do not enter complete remission at this time-point. The addition of rituximab may be considered.

- The role of interferon-alpha is nowadays limited to patients who present with severe pancytopenia, particularly low neutrophil and platelet counts. A regimen of 3 mega units 3 times a week will gradually improve blood counts and facilitate the subsequent use of either nucleoside analogue.

- There may still be some role for splenectomy in the management of HCL. If a patient is splenectomised, it is important to wait for the full benefits of the splenectomy to be apparent before starting any other therapy. It is therefore recommended to wait for at least 6 months after splenectomy.

- In the rare cases of HCL with BRAF V600E mutation Vemurafenib may be beneficial. Individual funding request is required.

Relapse/refractory HCL

- Rituximab in combination with a purine analogue is recommended in the treatment of relapsed disease.
- The majority of relapsed patients achieve second remission when re-treated with either pentostatin or cladribine. The choice of agent may depend on the duration of the first remission: if short, i.e. < 3 years, use an alternative agent; if long, e.g. > 5 years, use same or other.
- There is a small group of patients who have good responses to either agent but tend to relapse at regular intervals (every 2–4 years) and continue to respond to either drug.
- Evidence in the few non-responders or the rare ones who become refractory suggests a lack of cross-resistance between pentostatin and cladribine.
- Patients who present with bulky abdominal lymphadenopathy or who develop this at relapse respond less well to either agent.

6 - Supportive management

- Patients receiving cladribine or pentostatin should receive acyclovir and cotrimoxazole prophylaxis to prevent herpes reactivation and pneumocystis infections respectively until lymphocyte count is >1.0 x 10^9/l.
- Patients receiving pentostatin or cladribine should receive irradiated blood components to prevent transfusion-associated graft-versus-host disease.
- Growth factors, e.g. G-CSF, could also be used to treat severe neutropenia (< 0.5 x 10^9/l) before, during and/or after the use of either pentostatin or cladribine.
Hairy Cell Leukaemia - Variant

Hairy cell leukaemia - variant is categorised separately from HCL in the 2008 WHO classification as it is likely to be unrelated. It responds less well to either cladribine and pentostatin or interferon. Monocytopenia is not a feature and white counts tend to be elevated 40-60 x 10^9/l. Lymphocytes are usually villous. The diagnosis should be confirmed by HODS.

Splenectomy can result in partial remission for some patients. Purine analogues +/- rituximab can be beneficial in some patients.

7 - Summary of Chemotherapy Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cladrabine</td>
<td>First and subsequent lines</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>First and subsequent lines</td>
</tr>
<tr>
<td>Interferon</td>
<td>First and subsequent lines</td>
</tr>
<tr>
<td>Rituximab</td>
<td>R-chemotherapy relapsed/refractory</td>
</tr>
</tbody>
</table>
Lymphoplasmacytic Lymphoma (LPL) is a B-cell clonal disorder with proliferation of plasmacytoid lymphocytes in bone marrow and peripheral blood which express surface and cytoplasmic Ig (usually IgM), B cell associated antigens and have cytogenetic rearrangement of Ig heavy and light chains. Less than 5% of LPL are Ig A, Ig G or non-secretory.

Waldenstrom’s macroglobulinaemia (WM) is a clinical syndrome occurring in patients with LPL characterised by a monoclonal Ig M paraprotein with morphological evidence of lymphoplasmacytic lymphoma, normocytic anaemia and in some patients, symptoms of hyperviscosity. In the UK the median age at presentation is 70 years with a median survival of 60 months. Clinical presentations include incidental finding, anaemia, systemic symptoms, hyperviscosity, lymphadenopathy, organomegaly, peripheral neuropathy, symptoms of cryoglobulinaemia Type I and II, bleeding diathesis, Cold Haemagglutinins Disease and organ dysfunction due to tissue deposition or amyloid and very rarely CNS involvement known as Bing – Neel syndrome.

**Diagnostic Criteria**

There are no uniform morphological criteria for diagnosing WM. Somatic mutations of MYD88 is seen in 90% of LPL/WM and maybe used for diagnosis when required.

Patients can be symptomatic and in need of treatment at low levels of Ig M <10g/l or bone marrow infiltration. A cryoglobulin should be suspected in symptomatic patients with an apparently low IgM

Diagnosis of presence of a LPL must be confirmed by HODS

A monoclonal IgM may be associated with a range of other haematological disorders including Ig M MGUS, lymphoma, CLL, primary amyloidosis, Ig M plasma cell myeloma (osteolytic lesions and hypercalcaemia, plasma cell phenotype, Ig H translocations) and cold agglutinins disease.

**Staging investigations**

- FBC + film
- Immunophenotyping peripheral blood (lymphocytosis > 10 x 10^9 / l)
- Direct Antiglobulin Test
- Plasma viscosity
- Renal and hepatic function
- Ca2+ ,phosphate and urate
- Serum Immunoglobulins
- Serum protein electrophoresis and immunofixation
- Cryoglobulins where appropriate (collect at 37º)
- Urinalysis for free light chains
- Serum free light chains are not currently routinely recommended
- Beta2microglobulin (prognostic)
- LDH (prognostic)
- B12,folate and iron studies to exclude other causes of anaemia
Bone marrow examination (aspirate and trephine) is usually the test on which the diagnosis is made.

Conventional cytogenetic analysis is not routinely recommended but testing for 14q32 translocation can help in diagnosing Ig M myeloma.

Lymph node or tissue biopsy where appropriate. Lymph node biopsy should be obtained if transformation to high grade lymphoma suspected.

Hepatitis B, C and HIV serology.

CT scan chest, abdomen and pelvis as a baseline for those planned for chemotherapy.

Baseline ophthalmology (retinal changes can occur at Ig M levels as low as 30 g/l and PV 3.0)

For those patients presenting with peripheral neuropathy nerve conduction studies and anti-myelin associated glycoprotein (MAG) serology should be checked.

Fat pad biopsy with Congo Red staining should be considered in patients presenting with peripheral neuropathy

**Prognosis**

The clinical course of patients with WM is very heterogeneous. It is usually an indolent NHL and often does not require treatment for many years. Median survival for WM/LPL is at least 7 years. When treatment is indicated WM tends to be chemo-responsive with long disease free intervals. Some patients are refractory or have short duration of remission. The International Prognostic Scoring System for WM (IPSSWM), based on initial response to alkylating agent or purine analogue or rituximab as first line therapy, identifies a number of factors which may be predictive of a poorer outcome or shorter remission.

<table>
<thead>
<tr>
<th>Prognostic Factors</th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 years</td>
<td>1 or less adverse characteristics and age 65 or less</td>
<td>2 adverse characteristics or age &gt; 65 years</td>
<td>&gt;2 adverse characteristics</td>
</tr>
<tr>
<td>Beta2-M &gt;3g/l</td>
<td>Hb &lt; 115g/l</td>
<td>Platelets &lt;100 x 10^9/l</td>
<td>27% of patients 87% 5 year survival</td>
</tr>
</tbody>
</table>

| Prognostic | Low Risk | Intermediate Risk | High Risk |
| Factors | | | |
| Age > 65 years | 1 or less adverse characteristics and age 65 or less | 2 adverse characteristics or age > 65 years | >2 adverse characteristics |
| Beta2-M >3g/l | Hb < 115g/l | Platelets <100 x 10^9/l | 27% of patients 87% 5 year survival | 38% of patients 68% 5 year survival | 35% of patients 36% 5 year survival |
**Treatment**

**Asymptomatic WM**

Asymptomatic patients are managed with watch and wait approach and follow up every 3-6 months.

**Symptomatic WM**

Indications for Treatment.

Therapy is indicated in symptomatic disease or where there is evidence of end organ damage with clinical evidence of:

- Paraprotein effect
  - Symptomatic Hyperviscosity
  - Peripheral neuropathy
  - Amyloid
  - Symptomatic cryoglobulinaemia

- Autoimmune cytopenias

- Marrow suppression
  - Hb <100g/l
  - Platelets <100x10^9/l

- Cold agglutinin disease

- Bulky or progressive lymphoma (exclude high grade transformation)

- Bulky or progressive splenomegaly

- Progression to high grade lymphoma

- Constitutional symptoms fever, night sweats, weight loss

**Plasma Exchange**

Used as a temporary intervention to gain rapid control prior to the effect of chemotherapy.

*Hyperviscosity syndrome* – spontaneous bleeding, neurological disturbance and retinopathy. 1-2 procedures are usually required, exchanging 1-1½ calculated plasma. In patients who are drug resistant this may be indicated as long term management.

Plasma exchange should also be considered in asymptomatic patients with high vascular risk irrespective of PV.

*Peripheral Neuropathy*

The evidence supporting plasma exchange for the treatment of peripheral neuropathy associated with an Ig M paraprotein is weak.

*Cryoglobulinaemia*

Although there are few studies, which consider the role of plasma exchange in the treatment of cryoglobulinaemia, there is a clear rationale for its use. The treatment room should be warm and blood warmers used in the cell separator circuit to prevent precipitation during the procedure.
First Line Therapies

There are no large randomised trials to guide treatment algorithms for WM. Individual treatment decisions need to be made on the basis of patient's performance status, comorbidities and the rapidity which disease control is clinically required. Where possible, patients should be offered entry into a clinical trial. There is consensus that **Rituximab** in combination with chemotherapy is among the most effective therapies and is advised in patients medically fit for treatment. It is associated with the risk of Rituximab-mediated flare (40-50% of patients on monotherapy) with worsening of Ig M related complications and should be used with caution in patients with symptoms of hyperviscosity and/or Ig M levels >40g/l. The flare can persist for several weeks. Omitting rituximab from first 1 or 2 cycles of combination therapy reduces the risk. Currently there is insufficient evidence for the benefit of maintenance Rituximab.

**Chlorambucil (CLB) with or without Prednisolone** is appropriate for the initial and subsequent treatment of WM particularly in older frail patients. Responses are slow but toxicities minimal provided doses are adjusted for cytopenias. Intermittent or continuous schedules are effective with no difference in overall survival. Continuous schedules have a higher incidence of myelodysplastic syndrome.

**Bendamustine** in combination with **Rituximab** is approved by the Cancer Drug Fund (CDF) for first line treatment of low grade non-Hodgkin lymphoma. Trials of R-Bendamustine have only included small numbers of WM patients and no benefit for overall survival has been shown but response rates are high and duration of response longer than R-CHOP. R-Bendamustine is well tolerated with a good toxicity profile and is recommended for medically fit patients including those over 65.

RCD Rituximab, Cyclophosphamide and Dexamethasone

RCD is an alternative to R-Bendamustine also well tolerated.

**Purine Analogues**

Purine analogues are appropriate for the initial and subsequent treatment of Waldenstrom’s Macroglobulinaemia, either single agent or in combination e.g. **fludarabine and cyclophosphamide**. There is evidence for high response rates in both relapsed and primary untreated settings. Treatment related deaths due to infection reported at 3%. Prolonged lymphopenia arises requiring pneumocystis prophylaxis during and for 6 months post treatment. Purine analogues should be avoided in patients potentially considered for stem cell collection. The addition of Rituximab is appropriate in medically fit patients but can produce more profound neutropenia which may persist for up to 24 months after 6 cycles of FCR.

**Bortezomib**

Bortezomib is approved by Cancer Drug Fund for 2nd and subsequent line of therapy in patients who have received prior therapy with alkylating agents or purine analogues. The combination with dexamethasone is synergistic and a twice or once weekly schedule is appropriate. Aciclovir prophylaxis against Herpes Zoster is advised and careful evaluation for development of peripheral neuropathy.

**Combination Chemotherapy**

Combination chemotherapy with either CVP or CHOP is appropriate for the initial and subsequent treatment of WM. The addition of Rituximab to CHOP has been found to be superior to CHOP alone in WM. In general it is reserved for high grade transformation but it can be considered for patients with bulky disease if rapid response is required.
ESHAP chemotherapy may be used in resistant disease or prior to autologous transplant.

**Monoclonal Therapies**

Rituximab in combination is regarded as a standard of care. Single agent Rituximab is less effective in WM than Follicular lymphoma, and response can be slow.

Rituximab has a role in the treatment of progressive Ig M related peripheral neuropathy. Randomised studies have shown a 20 – 30 % absolute improvement on Rituximab compared to placebo.

**Thalidomide**

Thalidomide is of potential use in the treatment of patients who have previously received alkylating agents, purine analogues and antibody therapy.

**High Dose Therapy**

High dose therapy supported by autologous stem-cell transplantation has a role in the management of selected patients with WM with primary refractory or relapsed disease. Medically fit patients with remission duration less than two years should be considered for stem cell transplant. Allogeneic transplant may be suitable in younger patients with relapsed disease and should be discussed at the MDT on a case by case basis.

**Summary of chemotherapy regimens**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Indications</th>
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<tbody>
<tr>
<td>Oral Chlorambucil</td>
<td>First and subsequent line</td>
</tr>
<tr>
<td>Oral Fludarabine</td>
<td>First and subsequent line</td>
</tr>
<tr>
<td>Fludarabine and cyclophosphamide</td>
<td>First and subsequent line</td>
</tr>
<tr>
<td>CVP</td>
<td>First and subsequent line</td>
</tr>
<tr>
<td>RCD</td>
<td>First and subsequent line</td>
</tr>
<tr>
<td>CHOP</td>
<td>First and subsequent line</td>
</tr>
<tr>
<td>ESHAP</td>
<td>Relapsed or refractory disease prior to stem cell harvesting</td>
</tr>
<tr>
<td>Rituximab</td>
<td>First line in combination Second and subsequent line in combination or single agent</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Second and subsequent line</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>First and subsequent line</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Third and subsequent line</td>
</tr>
</tbody>
</table>
Lymphoplasmacytic Lymphoma / Waldenstroms Macroglobulinaemia

**Staging and Decision to Treat**

- **Asymptomatic**
  - Watch and Wait
  - **Symptomatic**
    - **Medically Fit**
      - Consider Clinical Trial
      - Rituximab + Chemotherapy eg Rituximab/Bendamustine
      - Fludarabine/Rituximab
      - Fludarabine, Cyclophosphamide, Rituximab
      - R-CHOP
      - In case of hyperviscosity consider plasmapheresis before Rituximab

- **Symptomatic**
  - **Medically Fit**
    - Consider Clinical Trial
  - **Medically Frail**
    - Chlorambucil +/- Rituximab
    - Fludarabine single agent
    - Rituximab single agent
    - In case of hyperviscosity consider plasmapheresis before rituximab

**Relapse**

- **Symptomatic**
  - **Medically Fit**
    - Consider Clinical Trial
  - **Medically Frail**
    - Consider Clinical Trial

- **Rituximab + Chemotherapy**
  - Response > 12 months: Repeat first line treatment
  - Response < 12 months: change to alternate Rituximab + chemotherapy
  - Response < 12 months and aggressive clinical course: consider ASCT
  - 2nd relapse, failure after ASCT: discuss allograft.

- **Mild rituximab chemotherapy combination or chemotherapy alone eg chlorambucil, fludarabine, bendamustine**
  - Bortezomib and Dexamethasone
  - Thalidomide (3rd line)