Clinical Guidelines for Lymphoid Diseases – Lymphoma and CLL

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Version History

Version	Date Issued	Brief Summary of amendments	Owner's Name:
3	May 2017	Diffuse Large B Cell Lymphoma updated	Dr J Wright
4	May 2018	Recommendation for all appropriate Lymphoma Regimes updated	Dr J Wright
		Bone Marrow Trephine Biopsy HODS examination section removed	Dr N J Morley
		Classical Hodgkin Lymphoma relapse updated – including updated Regimen list	Dr J G Wright
		Updated summary of regimens for Nodular Lymphocyte predominant Hodgkin Lymphoma	Dr J G Wright
		Diffuse Large B cell Lymphoma updated, including relapse and summary of regimens	Dr J G Wright
		Follicular Lymphoma updated	Dr J G Wright
		CLL update	Dr H Barker
		Waldenstroms Macroglobulinaemia updated	Dr H Barker
5	May 2019	NICE guidance on Venetoclax in CLL	Dr H Barker
		p53 testing and Ibrutinib in Waldenstroms Macroglobulinaemia	Dr H Barker
		Bortezomib for 2nd line treatment of Waldenstroms removed	Dr H Barker
		Splenic Marginal Zone Lymphoma added	Dr R Cutting
		Management of Primary Central Nervous System Lymphoma	Dr N Morley
		Available trials added	Dr Y Sorour
		NICE recommendations updated	Dr Y Sorour
		New NICE guidance on Pembrolizumab	Dr J Wright

(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

WHO classification of tumours of haematopoietic and lymphoid tissue; Ed Swerdlow SH, Campo E et al. 4th Edition. IARC press 2008.

British Committee for Standards in Haematology. Best practice in lymphoma diagnosis and reporting. http://www.bcshguidelines.com/pdf/best_practice_lymphoma_diagnosis.pdf

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 monoclone, ?MGUS, Diagnosis or follow-up of plasma cell myeloma

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

Investigation ?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.

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**.**

Lymphoma Chemotherapy and Fertility

	Infertility Rate	
Regimen	Azoospermia	Persistent amenorrhoea
ChIVPP/MOPP	>80%	<20%
ABVD	<10%	<10%
BEACOPP	>90%	<20%
Stanford V	>40%	<20%
CHOP (or CHOP-like)	<30%	<10%
ESHAP	>80%	>40%
IVE	>80%	>40%
High Dose	>90%	>80%

Staging using FDG-PET-CT

Staging

- Offer FDG-PET-CT imaging to confirm staging for people diagnosed with: stage I diffuse large B-cell lymphoma by clinical and CT criteria. PET staging is not mandated in more advanced disease but is recommended locally as it improves the interpretation of end of treatment scans.
- stage I or localised stage II follicular lymphoma if disease is thought to be encompassable within a radiotherapy field
- stage I or II Burkitt lymphoma with other low-risk features.
- For people diagnosed with other subtypes or stages of non-Hodgkin's lymphoma not listed in recommendation consider FDG-PET-CT imaging to confirm staging if the results will alter management.

Assessing response to treatment for diffuse large B-cell lymphoma

Do not routinely offer FDG-PET-CT imaging for interim assessment during treatment for diffuse large B-cell lymphoma.

End-of-treatment assessment

Offer FDG-PET-CT imaging to assess response at completion of planned treatment for people with:

Non-Hodgkin’s lymphoma: diagnosis and management (NG52)

Diffuse large B-cell lymphoma

Burkitt lymphoma.

For people with other subtypes of non-Hodgkin's lymphoma not listed in recommendation do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment unless the results will alter management.

Consider FDG-PET-CT imaging to assess response to treatment before autologous stem cell transplantation for people with high-grade non-Hodgkin's lymphoma.

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(NICE TA446) 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 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.

Nivolumab is recommended, within its marketing authorisation, as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults after autologous stem cell transplant and treatment with brentuximab vedotin (NICE TA462).

Pembrolizumab has recently been given NICE approval (NICE TA540) but is not recommended for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had autologous stem cell transplant and brentuximab vedotin. It may, however be used within the Cancer Drugs Fund as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had brentuximab vedotin and cannot have autologous stem cell transplant, only if:

- pembrolizumab is stopped after 2 years of treatment or earlier if the person has a stem cell transplant or the disease progresses.

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

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Regimen	Indication
ABVD/AVD	First line curative
VEPEMB	First line curative
DHAP	Second line curative
ESHAP	Second line curative
IVE	Third line curative
Gemcitabine and Oxaliplatin	Second and subsequent line palliative
VEDex	First and subsequent line palliative
ChlVPP	Second and subsequent line palliative
Brentuximab	Following autologous stem cell transplantation Third line unfit for transplant
Nivolumab	Following autologous stem cell transplant and breuntuximab

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 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

Regimen	**Indication**
ABVD	First or second line advanced stage
R-CHOP	First or second line advanced stage
ESHAP	Second or subsequent line
DHAP	Second or subsequent line
BEAM	Second or subsequent line

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 (see also NICE Guideline on management of reflux).

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, 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 R-chlorambucil and R-Fludarabine.
Local radiotherapy can be offered for bulky symptomatic disease.

Transformation to DLBCL- should be treated just as for de novo DLBCL

Splenic Marginal Zone Lymphoma

Treatment options include observation if asymptomatic, palliative radiotherapy to the spleen, single agent Rituximab (four weekly 375mg/m^2 doses), or combination chemotherapy (R-CVP, R-Clorambucil etc).

Diffuse Large B cell Lymphoma (DLBCL)

1. Diagnostic Criteria

All patients should have their diagnoses confirmed by HODS.

2. Recommended Staging Investigations

Blood tests

FBC
U/E's, LFT's, Ca, LDH, serum urate, serum immunglobulins.
Viral serology for HIV, Hepatitis B and C
Bone marrow biopsy *'*
Consider marrow biopsy if unexplained cytopenias, PET-CT unavailable or histologically discordant disease suspected'

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.
Apart from in suspected stage 1 disease, PET-CT is not mandated as a staging investigation but will assist reporting radiologists with correct interpretation of end of treatment PET..
WHO/ECOG performance status.
Calculation of International Prognostic Index (IPI).

3. Primary Treatment

Non-bulky Stage IA (PET confirmed)

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).

In frail patients consideration may be given to the use of R-PMitCEBO or miniRCHOP 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 immunsuppression 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

Explain to people with diffuse large B-cell lymphoma that they have an increased risk of central nervous system lymphoma if the testis, breast, adrenal gland or kidney is affected.

Explain to people with diffuse large B-cell lymphoma that they may have an increased risk of central nervous system lymphoma if they have 2 or more of the following factors:

- elevated lactate dehydrogenase (LDH)
- age over 60 years
- poor performance status (ECOG score of 2 or more)
- more than one extranodal site involved
- stage III or IV disease.[I] - Information. Explain that the level of risk increases with the number of factors involved.

Offer central nervous system‑directed prophylactic therapy to people with diffuse large B-cell lymphoma: involving testis, breast, adrenal gland or kidney **or** who have 4 or 5 of the factors associated with increased risk of central nervous system relapse listed above..

CNS Prophylaxis: In patients of adequate performance status HD methotrexate 3.5g/m2 with folinic acid rescue on day 15 after courses 2 and 4 RCHOP should be administered. It is crucial to maintain RCHOP dose intensity. Consider use of GCSF support. Consider brief deferral of Methotrexate if reversible risk factors for increased toxicity present (e.g. effusions, use of NSAIDs/Beta-Lactam antibiotics, transient liver/renal abnormalities).

If acute renal dysfunction (oliguria, rapidly rising creatinine in context of reduced clearance of Methotrexate) develops, consideration to the use of Glucarpidase should be made (available on named patient basis).

In patients >70 yrs or with impaired renal function consideration should be given to methotrexate dose attenuation to a minimum of 1.5g/m2.

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-GDP/ 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 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 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.

CAR-T Cell Therapy

Axicabtagene-ciloleucel/Tisagenlecleucel (NICE TA567/559) can be offered to patients with relapsed or refractory Diffuse Large B-Cell Lymphoma following 2 or more systemic therapies, following MDT discussion.

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

Regimen	**Indications**
R-CHOP	First line (additional Methotrexate 3.5g/m2 x2 for testicular lymphoma)
R-PMitCEBO	First line elderly/frail
R-CODOX-M/R-IVAC	First line high risk
R-GDP	Second or subsequent line
R-DHAP	Second or subsequent line
IVE	Third line
GemOx	Third or subsequent line
VEDex	First and subsequent line palliative

Burkitt Lymphoma

Key issues

- CODOX-M/IVAC plus Ritixumab remains the best available treatment
- 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).
- PET scan to confirm stage I/II disease. Follicular lymphoma is generally PET avid and this imaging maybe considered for more advanced disease but 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.

All other patients

- Active monitoring / watch and wait in asymptomatic patients.
- Single agent rituximab induction may also be considered in asymptomatic patients with stage 3 or 4 disease (NICE technology appraisal guidance 243).
- Rituximab containing regimen e.g.6 courses of R-CVP, R-CHOP or R-Bendamustine to be followed by rituximab maintenance 2 monthly for 2 years (NICE technology appraisal guidance 226).
- 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 in follicular lymphoma
- Histological grade 3B should be treated as DLBCL with R-CHOP
- Obinutuzumab as first line option for advance Follicular Lymphoma (NICE technology appraisal guidance 513)with chemo and then maintenance.

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 maybe 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
- R-CHOP 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 or allograft may be of benefit and cases should be discussed at the regional MDT and/or Lymphoma review meeting.
- Do not offer consolidation with high-dose therapy and autologous or allogeneic stem cell

transplantation to people presenting with concurrent diagnoses of follicular lymphoma and diffuse large B-cell lymphoma that have responded to first-line treatment

Relapsed Follicular NHL

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

Consider available clinical trial if available – currently open at STH – ReBEL and Citadel 203

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 (NICE technology appraisal guidance 137).

Obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance is recommended as an option for treating adults with follicular lymphoma that did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen (NICE technology appraisal guidance 472.)

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

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.

Consolidation with stem cell transplantation

- Offer consolidation with autologous stem cell transplantation for people with follicular lymphoma in second or subsequent remission (complete or partial) who have not already had a transplant and who are fit enough for transplantation.
- Consider consolidation with allogeneic stem cell transplantation for people with follicular lymphoma in second or subsequent remission (complete or partial): who are fit enough for transplantation and for whom a suitable donor can be found and when autologous stem cell transplantation has not resulted in remission or is inappropriate (for example, because stem cell harvesting is not possible).

Guidelines for the Management of Primary Central Nervous System Lymphoma (PCNSL)

These guidelines are based on BCSH 'Guidelines for the diagnosis and management of Primary Central Nervous System Diffuse Large B Cell Lymphoma.' BJHaem 2019,184, 348-363.

Diagnosis

A biopsy is required in all patients prior to treatment.
Prior to initial biopsy steroids should be avoided
All patients should have their diagnosis confirmed by HODS

Initial Assessment

Contrast enhanced MRI is the optimal imaging modality pre-treatment and for response assessment.
Patients should have a slit assessment to look for intraocular disease.
Routine staging includes,

- PET scan to exclude systemic disease
- Blood tests should include FBC, U/E's, LFT's and LDH.
- Viral serology including HepBSAg, HepBcAb, Hep C and HIV
- Men should undergo testicular ultrasonography

Patients requiring systemic chemotherapy will require a central venous access device

Initial Treatment

Should be considered on a case by case basis depending on patient fitness and co-morbidities.
For those less fit consider sequential high dose Methotrexate (HD MTX) followed by high dose Cytarabine (HiDAC).
For those fit enough consider up to 4 cycles of MATRix chemotherapy. The doses of Cytarabine and Thiotepa may need to be reduced as tolerated.
MATRix is an intensive regimen and patients should receive G-CSF support, prophylactic Aciclovir and Pentamidine nebulisers.

Consolidation Treatment

For those with chemo-responsive disease and who are fit enough, consider autologous stem cell transplant (ASCT) with Carmustine and Thiotepa conditioning.

Whole Brain radiotherapy (WBRT) can be used in those with inadequate response to chemotherapy or who are not fit for ASCT but is associated with a risk of cognitive decline.

Patients with concurrent ocular involvement should also be considered for bilateral ocular radiotherapy if ineligible for ASCT or not in CR following ASCT.

Relapse/Refractory Disease

Options include TIER chemotherapy, palliative WBRT or symptomatic treatment with steroids only.

Follow-up

Response assessment with contrast enhanced MRI 1-2 months after completion of consolidation therapy.
Routine surveillance imaging in those patients achieving a CR is not recommended.

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

fit for PBSCT,
R-CHOP alternating with R-DHAP (or R-ESHAP) followed by PBSCT and maintenance rituximab every 2 months for up to 3 years.

not fit for PBSCT:
R- Bendamustine
R-CVP
R-CHOP
R-FC
VR-CAP

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

Patients should also receive 2 monthly maintenance rituximab until progression.

Management of relapsed MCL

Ibrutinib as per CDF conditions is the first choice for relapsed disease..

Summary of treatment regimens for MCL

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

** 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.

Anaplastic large cell lymphoma	standard treatment is with 6# CHOP.
Peripheral T cell lymphoma NOS	standard treatment is with 6# CHOP.
Angio-immunoblastic lymphoma	standard treatment is with 6# 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, cytopenias or disease related symptoms. A 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.

17. 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 and P53 deletion by molecular genetics
International and national guidelines all recommend testing for TP53 disruption prior to each line of therapy.

iWCLL 2018	Assessment of both del(17p) and TP53 mutation should guide therapeutic decisions in routine practice and should be repeated prior to any subsequent, second- or third-line of treatment
BCSH 2018	Tests for TP53 disruption should be performed on all patients prior to each line of therapy, should include both mutation and deletion detection and ideally should also reveal subclonal TP53 mutations
ESMO 2015	FISH for detection of del(17p) and in the absence of del(17p), molecular genetics for detection of TP53 mutations (at least exons 4–10, eventually exons 2–11). FISH and TP53 mutation analyses should be repeated before relapse treatment is administered
ERIC 2016	ERIC recommends TP53 mutation analysis at each progression requiring treatment (minimum exons: 4–9; optimum exons 2–11)

- When booking into HODS, please select TP53 mutational testing (by HTS) in addition to TP53 deletion testing (by FISH)
- In partnership with an ISO accredited lab in Oxford, Janssen has agreed to reimburse the cost of NGS TP53 mutation testing for CLL patients.

- 2 EDTA samples are required for mutational testing (as required by Oxford lab)
- 1 EDTA or 1 Lithium heparin for TP53 deletion testing (at SDGS)
- If immunophenotyping is also required, ideally another sample in EDTA is preferred. If not possible, FCM can be done on one of the EDTA sample sent for TP53 mutational testing. **However, please be aware that this will cause a delay in the sample being sent to Oxford.**
- Completed request form (Link on HODS front page)

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. • NICE guidance recommends Ibrutinib for patients who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable or Idelalisib and Rituximab. If patient is unsuitable for a B cell receptor pathway inhibitor or has progressed on a BCR inhibitor Venetoclax monotherapy is recommended by NICE. Patients who have progressed on a BCRI can also be considered for Venetoclax plus rituximab therapy for 2 years. 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 including core antibody, Hepatitis 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.

Binet Stage	**Organ involvement**	**Hb g/l**	**Platelets**
A	0-2 areas	>100	>100
B	3-5 areas	>100	>100
C	NA	<100 and /or	<100

Rai Stage	Risk Group	
0	Low	Lymphocytosis only
1		Lymphadenopathy
II	Intermediate	Hepatomegaly or splenomegaly +lymphocytosis
III/IV	High	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 30x109/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.

5. 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

NICE guidance recommends first line treatment with B cell receptor (BCR) signalling pathway inhibitor such as Ibrutinib (NICE approved TA429) or Idelalisib and Rituximab (NICE approved TA359). Venetoclax monotherapy is indicated in patients where a BCRI is unsuitable. Alemtuzumab +/- steroids is an alternative for patients considered fit enough but rarely indicated now the BCR inhibitors are available. 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 loss of p53

B cell receptor signalling pathway inhibitors such as Ibrutinib or Idelalisib are suitable for the treatment of less fit patients with loss of p53. Ibrutinib. and Idelalisib and Rituximab are NICE approved.

1st Line treatment of patients with loss of P53 for whom BCR Inhibitor is unsuitable

Venetoclax is available through the Cancer Drug Fund for patients with a 17p deletion or TP53 mutation and when a B- cell receptor pathway inhibitor is unsuitable

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.

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

Both Chlorambucil and Ofatumumab and Chlorambucil and Obinutuzumab are approved by NICE for first line treatment of less fit patients if they are unsuitable for Bendamustine . Combination of chlorambucil with one of these anti CD20 monoclonal antibodies has improved progression free survival and duration of first remission.

Chlorambucil and Rituximab are also available for first line treatment of less fit patients . The progression free survival and duration of first remission is expected to be shorter than with the new anti CD20 antibodies.

Maintenance Therapy

Maintenance therapy in patients after 1st line chemo-immuno therapy is currently under investigation in clinical trials but is not routinely recommended

6. 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 Idelalisib 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. Idelalisib and Rituximab is NICE approved (TA359). Ibrutinib is NICE approved (TA 429). Individual patient factors need to be taken in to 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 Idelalisib 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.

Relapse following BCR Inhibitor therapy

Venetoclax is recommended for use within the Cancer Drug Fund for patients whose disease has progressed after a B- cell receptor pathway inhibitor or without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo- immunotherapy and a B- cell receptor pathway inhibitor. Venetoclax-rituximab therapy with discontinuation of Venetoclax after 2 years therapy is NICE approved through registration on CDF for relapse following BCRI therapy

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 who are 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 alemtuzumab 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 immunosupressive treatment . The summary of product characteristics recommends pneumocystis prophylaxis throughout treatment with Idelalisib and for 2-6 months on discontinuation. Pneumocystis prophylaxis should be considered for patients on Ibrutinib.

Regular CMV monitoring and 2 weekly full blood counts are also recommended in first 6 months of treatment with Idelalisib.

8. Summary of chemotherapy regimens

Regimen	Indications
Oral chlorambucil	First and subsequent line less fit
FCR	First line intensive Second and subsequent line (not previous received Rituximab)
Bendamustine+Rituximab	First line
Ibrutinib	1st Line p53 deleted Second and subsequent line
Idelalisib + Rituximab	1st Line p53 deleted Second and subsequent line
Fludarabine, Cyclophosphamide, Rituximab	Second and subsequent line
CHOP	Second and subsequent line
Bendamustine	Second and subsequent line
R-Bendamustine	Second and subsequent line

High dose methylprednisolone	Third and subsequent line P53 deleted CLL first and subsequent line
Alemtuzumab	Third and subsequent line P53 deleted CLL first and subsequent line
FLAIR trial	Fit non p53 deleted first line
Venetoclax	1st line for patients with with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable, or whose disease has progressed after a B-cell receptor pathway inhibitor 3rd line •without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo immunotherapy and a B cell receptor pathway inhibitor
Venetoclax-R	Venetoclax plus rituximab is indicated 'for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

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 agent 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 cladrabine 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 109/l) before, during and/or after the use of either pentostatin or cladribine.

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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 cladrabine 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

Regimen	**Indications**
Cladrabine	First and subsequent lines
Pentostatin	First and subsequent lines
Interferon	First and subsequent lines
Rituximab	R-chemotherapy relapsed /refractory

Management of Lymphoplasmacytic Lymphoma /Waldenström's Macroglobulinaemia

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.

Waldenstroms 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 cryogobulin 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 anaeamia

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.

Prognostic Factors	**Low Risk**	**Intermediate Risk**	**High Risk**
Age > 65 years Beta2-M >3g/l M-Protein >70g/l Hb < 115g/l Platelets <100 x 10^9/l	1 or less adverse characteristics and age 65 or less	2 adverse characteristics or age > 65 years	>2 adverse characteristics
	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.

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.

2nd Line therapy-

Ibrutinib

Ibrutinib is recommended by NICE TA491 for use in the Cancer Drugs Fund as an option for treating Waldenstrom's macroglobulinaemia in adults who have had at least 1 prior therapy, only if the conditions in the managed access agreement for ibrutinib are followed

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

Regimen	Indications
Oral Chlorambucil	First and subsequent line
Oral Fludarabine	First and subsequent line
Fludarabine and cyclophosphamide	First and subsequent line
CVP	First and subsequent line
RCD	First and subsequent line
CHOP	First and subsequent line
Ibrutinib	2nd line
ESHAP	Relapsed or refractory disease prior to stem cell harvesting
Rituximab	First line in combination Second and subsequent line in combination or single agent
Bendamustine	First and subsequent line
Thalidomide	Third and subsequent line

Lymphoplasmacytic Lymphoma / Waldenstroms Macroglobulinaemia