Lancashire and South Cumbria Haematology CRG Guidelines
Chronic Lymphocytic Leukaemia

These guidelines are to be used in conjunction with the BCSH guidelines 2022, ESMO guideline 2015, Good Practice Guidance on the management of Richter transformation (RT) of CLL 2021 and NICE recommendations.

DIAGNOSIS

The diagnosis of chronic lymphocytic leukaemia (CLL) is based on lymphocyte morphology, the presence of more than 5 x 10^9/l circulating clonal B cells for > 3 months and characteristic immunopenotype. CLL is a chronic leukaemia of CD 5+ B-cells.

All diagnoses to be reviewed at HMDS where treatment indicated or diagnosis is unclear but diagnosis on local flow cytometry is acceptable for early stage, asymptomatic patients.

DIFERENTIAL DIAGNOSIS

- Monoclonal B-lymphocytosis" (MBL) is diagnosed in individuals with less than 5x 10 ^{9}/l lymphocytes present either with the phenotype of chronic lymphocytic leukemia (CLL), atypical CLL, or non-CLL (CD52) B cells in the absence of other lymphomatous features and without other symptoms (lymphadenopathy, organomegaly, cytopenias and general symptoms). Precedes virtually all cases of CLL/small lymphocytic lymphoma (SLL).

  - Low-count MBL is defined as a PB with low lymphocyte and B cell counts (usually < 0.5x 10^9/L). Very low risk of progression (if any). No indication to monitor even if detected incidentally.

  - High-count MBL. High lymphocyte and B cell counts (≥ 0.5x 109/L). Requires routine/yearly follow-up, annual progression requiring treatment 1-2%. Has

very similar phenotypic and genetic/molecular features as Rai stage 0 CLL, although high risk cytogenetic alterations (5-9%), immunoglobulin heavy chain variable region (IGHV)- mutated cases are more frequent in MBL.

- Non-CLL type MBL. Early stage of splenic marginal zone lymphoma

- Small lymphocytic lymphoma (SLL). Lymph node involvement by SLL. B-cells may be present in lymph nodes and lymphoid tissue such as the spleen and the tonsils. No significant rate of progression. The number of B lymphocytes in the peripheral blood should not exceed 5 x 10^9/L. In SLL, the diagnosis should be confirmed by histopathology of a lymph node biopsy.

- Mantle cell lymphoma
- Lymphoplasmacytic lymphoma (Waldenstrom's Macroglobulinaemia)
- Hairy cell leukaemia
- Large granular lymphocyte leukaemia
- Mycosis fungoides
- Adult T cell lymphoma leukaemia
- Prolymphocytic leukaemia.

STAGING

Binet Staging System:

- A: two of less lymphoid areas enlarged.
- B: three or more lymphoid areas enlarged.
- C: Presence of anaemia (Hb <100) or thrombocytopenia (Plat <100).

INVESTIGATIONS

Essential:

- Full blood count
- Immunophenotyping of peripheral blood
- Direct antiglobulin test (DAT) and reticulocyte count
- Serum immunoglobulins levels, serum protein electrophoresis.
- LDH.
- U&E, creatinine, urate, calcium, phosphate.

- Liver function test.

Indications for treatment:

1. Anaemia (Hb < 10 g/dl) and thrombocytopenia (<100 x 10^9/l) due to bone marrow infiltration by CLL.
2. Progressive, symptomatic splenomegaly (>6 cm below costal margin).
3. Progressive, symptomatic lymphadenopathy (cluster >10cm diameter).
4. Progressive lymphocytosis with the increase of lymphocyte number more than 50% over 2-months or lymphocyte doubling time less than 6 months.
5. Autoimmune anaemia and thrombocytopenia not responsive to standard treatment.
6. B symptoms: weight loss more than 10% in previous 6 months, extreme fatigue, fever >38 o for more than 2 weeks without evidence of infection.

Recommended tests in symptomatic patients:

- Bone marrow test is not necessary in patient with stage A CLL. Recommended:
  - For trials propose.
  - In case of phenotypically atypical CLL.
  - For investigation of cytopenia in CLL.
- CT scans are not recommended at diagnosis. Recommended:
  - When suspicious of high-grade lymphoma transformation.
  - Before treatment to assess risk of TLS.
  - For trials propose.
- TP53 disruption by FISH and NGS before every line of treatment.
- IGHV gene mutation analysis if FCR chemotherapy is considered.
- Lymph node biopsy when diagnosis is no certain and/or to exclude transformation.
- Screen for hepatitis B or C infection prior to therapy.
- HLA typing for possible allogenic transplant candidates.

Bone marrow aspirate, cell markers, trephine and peripheral blood sample (EDTA) to be sent to HMDS Leeds.

DEFINITIONS OF RESPONSE, RELAPSE, REFRACTORY AND PROGRESSIVE DISEASE

IWCLL criteria for complete response (CR), partial response (PR) and progressive disease are shown in table below.

The IWCLL define **relapse** as disease progression at least 6 months after achieving a CR or PR. **Refractory** disease is currently defined as treatment failure or disease progression within 6 months of anti-leukaemic therapy. However, the duration of response that should influence the choice of second line therapy is an area of continuing debate (Zenz et al, 2012).

Parameter	Group	CR	PR	PD
Lymphadenopathy	A	None > 1·5 cm	Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly	A	None	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	A	None	Decrease ≥ 50%	Increase ≥ 50%
Blood Lymphocytes	A	<4·0 × 10⁹/l	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline
Marrow	A	Normocellular, < 30% lymphocytes, no B-lymphoid nodules	50% reduction in marrow infiltrate or B-lymphoid nodules	
Platelet count	B	>100 × 10⁹/l	>100 × 109/l or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Haemoglobin	B	>110 g/l	>11 g/dl or increase ≥ 50% over baseline	Decrease of >20 g/l from baseline secondary to CLL
Neutrophils	B	>1·5 × 10⁹/l	>1500/µl or >50% improvement over baseline	

CR: complete response: all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR: partial response: at least two of the criteria of group A plus one of the criteria of group B have to be met; stable disease is absence of progressive disease (PD) and failure to achieve a PR. The International Workshop on Chronic Lymphocytic Leukaemia has recently agreed that blood lymphocytosis alone should not be a criterion for disease progression or relapse, based on the lymphocytosis observed in patients treated with BcR signalling inhibitors in the absence of disease progression.

MANAGEMENT

MBL-CLL.

These patients have a low risk of developing progressive disease.

The clinical assessment of CLL symptoms is indicated. The monitoring of FBC is recommended every 3-6 months in the first year and if stable once a year later (preferably in the local surgery with clinical protocol provided).

Low-count MBL (usually < 0.5x 109/L). Very low risk of progression (if any). No indication to monitor even if detected incidentally.

SLL

SLL should be managed in the same manner as CLL.

CLL Early stage (Binet's stage A)

Clinical assessment and FBC monitoring preferably in GP surgery. No treatment indicated regardless of prognostic markers.

Stage A patients who develop AIHA or ITP in the absence of disease progression should be treated in the standard way for the autoimmune phenomenon but not requires cytoreductive therapy. Also, hypogammaglobulinaemia is not an indication for therapy.

Patients with early CLL should be reviewed at least twice within the first year from diagnosis to assess the rate of disease progression. For those with stable disease, particularly if they have 'good risk' clinical and/or laboratory features, monitoring can be extended to an annual check. This may be performed in primary care with provided clinical protocol containing indication for re referring to haematology.

Initial therapy for advanced, symptomatic CLL. Without aberrant TP53

Eligible patients should be entered into clinical trials.

Fit patients:

- Obinutuzumab / Venetoclax via the Cancer Drugs Fund (CDF).
- Fludarabine plus cyclophosphamide and rituximab (FCR) can be considered if mutated IGHV.

Less fit patients (or unsuitable for FCR):

- Obinutuzumab-Venetoclax if patient is unsuitable for fludarabine plus cyclophosphamide and rituximab (FCR).
- Acalabrutinib monotherapy.

- Chlorambucil - obinutuzumab is NICE approved, however Bendamustine or Chlorambucil-based chemoimmunotherapy are no longer recommended in BSH guideline.
- Corticosteroid monotherapy can be considered.
- Best supportive care.

Initial therapy for advanced, symptomatic CLL with aberrant TP53

- Bruton's tyrosine kinase (Btk) inhibitor Acalabrutinib or Ibrutinib in front-line is NICE approved.
- Obinutuzumab-Venetoclax via the cancer drugs fund.
- BCL2 inhibitor Venetoclax monotherapy for patients unsuitable for BtK inhibitor therapy.
- Idelalisib and rituximab combination therapy is NICE approved as a suitable alternative for patients for whom ibrutinib is deemed inappropriate. Because of severe infectious complications, the PI3K inhibitor idelalisib combined with rituximab is only recommended for frontline therapy in patients not suitable for any other therapies if anti-infective prophylaxis is taken and measures to prevent infection are followed.

Treatment of relapsed CLL

- Bruton's tyrosine kinase (Btk) inhibitor Acalabrutinib or Ibrutinib in patients with relapsed or refractory to chemo-immunotherapy, have relapsed after chemoimmunotherapy, or for whom re-treatment with chemoimmunotherapy is inappropriate.
- BCL2 antagonist Venetoclax in combination with Rituximab for patients who has received at least 1 prior therapy.
- Patients failing upon therapy with BCR inhibitors should preferentially be switched to a BCL2 antagonist when available. The second choice is a switch to another BCR inhibitor (e.g. from Btk inhibitor to PI3K inhibitor or vice versa).
- PI3K inhibitor Idelalisib in combination with rituximab when the disease has been treated but has relapsed within 24 months, or who are unsuitable for or who are refractory to BTKi- and BCL2i-based treatment.
- Allogenic bone marrow transplant should be considered in patients transplant-eligible, refractory to chemotherapy and/or carry TP53 disruption, and relapse following at least one targeted agent, or intact TP53 and BCL2i/BCRi relapse.
- Clinical trials.

Unfit patient can be offered best supportive care and referred to palliative care.

Management of Richter transformation (RT) of CLL

- The development of transformation into an aggressive lymphoma or Hodgkin's lymphoma (HD), a Richter's syndrome or B-cell prolymphocytic leukaemia (B-PLL) occurs in 2 –15% of CLL patients during the course of their disease.
- The diagnosis must be confirmed by lymph node excision.
- Risk factors include poor performance status, >2 prior therapies, >5 cm lymphadenopathy, clonal identity to the underlying CLL clone and loss or mutation of the TP53 gene.
- The outcome of CLL patients with lymphomatous transformation is significantly poorer than those patients presenting with de novo lymphomas with a similar histology.
- All patients with a clinical suspicion of transformed CLL and an SUVmax>5 should undergo PET-targeted biopsy of the most safely accessible 18F-FDG-avid site.
- Surgical excisional or incisional biopsy is strongly recommended to establish the diagnosis. Where this is not possible, a core needle biopsy is an alternative.
- The transformation of CLL into HD represents a separate entity, since conventional chemotherapy against HD often achieves long-lasting remissions. Otherwise, the prognosis of Richter's syndrome and B-PLL is very poor.
- Depending on the histological sub type of lymphomatous transformation, patients who are suitable for intensive therapy should receive regimens currently employed for either primary DLBCL or HL (preferably in the context of a clinical trial), followed by AlloSCT if eligible and high-risk features (TP53 disruption, partial metabolic response, prior CLL treatment, clonality related RT).
- CAR-T cell therapy (after 2 lines of treatment for RT).
- Because of the short response duration of Richter's syndrome, an allogeneic stem cell transplantation should be considered in patients with available donors and sufficient fitness.

Supportive care

1. Transfusion of blood products (irradiated lifelong for fludarabine treated patients).
2. Infections: Susceptibility is multifactorial and due to the disease, itself and as a result of therapy and includes hypogammaglobulinaemia, neutropenia, impaired T and natural killer cell function and defective complement activity.

3. Chemotherapy, immunotherapy with anti CD20 antibodies and transplantation may result in reactivation of hepatitis B and/or C virus infection. All patients with CLL receiving immunosuppressive therapy should be screened for evidence of previous hepatitis B or C infection. Patients positive for hepatitis B surface antigen (HBSAg) or hepatitis B core antigen (HBCAg) may require antiviral treatment and should be managed jointly with a specialist in viral hepatitis.
4. Antimicrobial prophylaxis as per local guideline. For patients taking BTKi continuously Pneumocystis jirovecii (PJP) prophylaxis is recommended either throughout therapy or for at least the first 12 months.
5. Granulocyte colony-stimulating factor may be useful in reducing the incidence of infection in patients receiving myelotoxic regimens.
6. Intravenous immunoglobulin infusion can be indicated in patients with recurrent infections and low IgG level. Indication:

   - Patients suffer recurrent or severe bacterial infections despite six months of continuous oral antibiotic therapy;
   - have a total IgG <4 g/l; and
   - have documented failure to respond to polysaccharide vaccine challenge (https://igd.mdsas.com/clini cal- info/).

   Subcutaneous preparations of immunoglobulin replacement therapy (scIg) that can be self-administered may be more convenient for patients and can be used as an alternative to intravenous preparations. A starting dose of 0.4–0.6 g/kg/month is recommended with adjustment according to the trough IgG (https://igd.mdsas.com/clinical-info/), aiming for a trough level of 6–8 g/l after 4 months of treatment. The immunoglobulin dose should be adjusted according to clinical response and trough levels repeated after three doses. Higher trough levels may be of benefit in patients with underlying co-morbidities, particularly bronchiectasis. *Monitoring*. Patients should be reviewed regularly, especially in the first 12 months of treatment. *Duration*. Treatment should be stopped if there is no improvement in the frequency or severity of bacterial infections after 1 year. If a decision to stop immunoglobulin replacement is made, this should take place over the summer months and be reviewed prior to the onset of winter. Patients should continue on prophylactic antibiotics.
7. Immunizations.
   a. At diagnosis: Vaccination with pneumococcal conjugate vaccine (PCV13, Prevnar) is recommended for all CLL patients, followed by PPV23 (Pneumovax II) at least 2 months later (irrespective of previous pneumococcal vaccinations) (JCVI, 2013, 2015, DOH, 2018). Serum antibody response to vaccination should be checked in those with a history of recurrent or severe bacterial infection. Patients who respond

to vaccination and subsequently develop recurrent bacterial infections should be revaccinated if S. pneumoniae and Hib antibody levels have fallen.

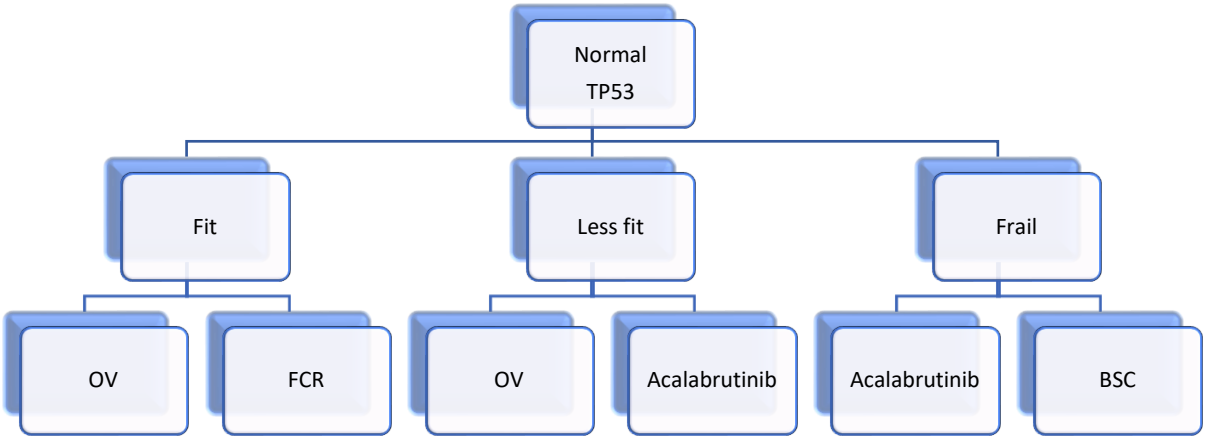
b. Annual vaccination against seasonal influenza and novel strains is recommended.
c. Live vaccines such as polio, H. zoster and yellow fever should be avoided.
d. Patients should avoid contact with children who have received the live nasal influenza vaccine for seven days.
e. The recombinant varicella vaccine (Shingrix) is safe for patients with CLL,67 and is available in the UK for those aged 70–79 years of age.
f. Vaccinations should be avoided, if possible, 2 weeks prior to, during or up to 6 months after chemo-immunotherapy.

8. COVID-19 vaccination is recommended in all patients and household members (UK DoH guidance). Routine testing for COVID-19 antibody is currently not recommended. Monoclonal antibody therapy against the spike protein (or anti-viral therapy if administration of monoclonal is not available) is recommended for patients who develop COVID-19 infection and are within five days of symptom onset.

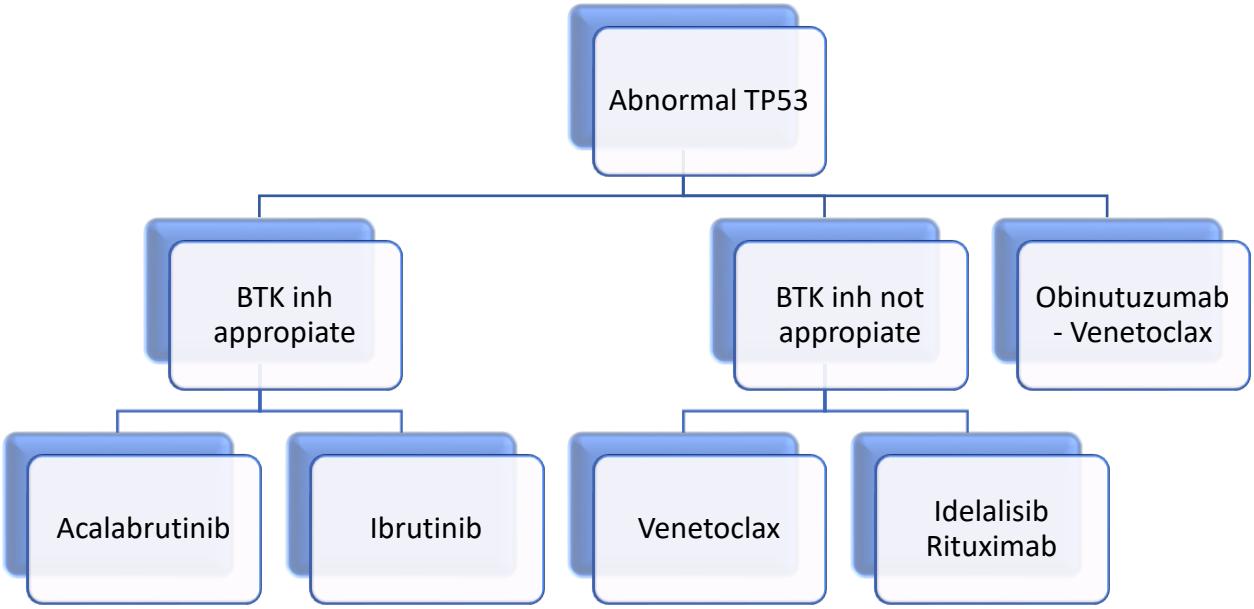
Follow-up

- Stage A patients with stable disease require review every 6-12 months depending on age etc. this can be undertaken by the GP in many cases with agreed triggers for referral back to the haematology team.
- Patients with progressive disease will require more frequent monitoring (1-3 monthly) depending on phase of change.
- Patients on treatment should be seen once every 1-4 weeks when started, then adjust according to treatment chosen and tolerance.
- Patients on F/U after completion of treatment should be seen monthly until recovery is secure and then every 3-6 months depending on clinical circumstances.

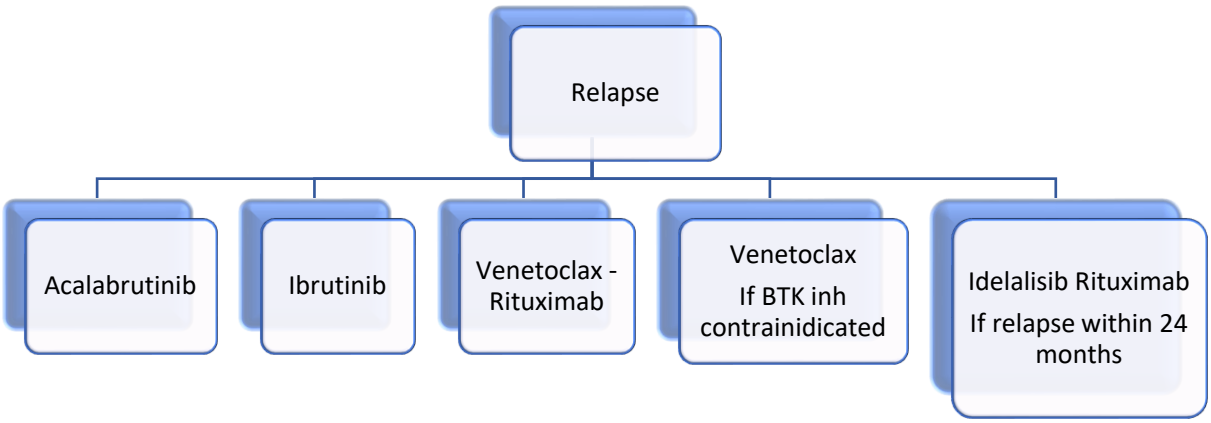
1. Appendix. CLL treatment - FIRST LINE – Normal TP53.



2. Appendix. CLL treatment - FIRST LINE. Abnormal TP53



3. Appendix. CLL treatment - **Refractory / Relapse CLL**



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