
Pan-London Haemato-Oncology Clinical Guidelines

Lymphoid Malignancies

Part 4: Chronic Lymphocytic Leukaemia (CLL)
and B-prolymphocytic Leukaemia (B-PLL)

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Lead authors 2020:

Dr Samir Agrawal, Barts Health NHS Trust

Dr Parag Jasani, University College London Hospitals NHS Foundation Trust

Professor Kikkeri Naresh, Imperial College Healthcare NHS Trust

Dr Piers Patten, King's College Hospital NHS Foundation Trust

Dr John Riches, Barts Health NHS Trust

2018 Edition;

Dr Samir Agrawal, Barts Health NHS Trust

Dr Piers Patten, King's College Hospital NHS Foundation Trust

Disclaimer

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

Contact us

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

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

1 Introduction

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in adults, with an incidence of 3–4 per 100,000 per year. Median age at presentation is 72 years and it occurs twice as frequently in males as females. There is a familial/genetic predisposition.

CLL is not usually curable. It typically develops slowly, with many people not needing treatment for months or years, and some not at all. Treatment can control the disease for many years. For all stages of CLL, on average 44 out of 100 men (44%) and 52 out of every 100 women (52%) will live for at least 5 years after being diagnosed, with the outlook depending on the stage of the disease when diagnosed.

B-prolymphocytic leukaemia (B-PLL) is a very rare aggressive leukaemia with poor survival rates. Morphology and immunophenotype are distinct from CLL although assessment and management are as for CLL.

2 Referral Pathways from Primary Care

In up to 70% of patients, the diagnosis of CLL is an incidental finding on full blood count (FBC).

*In asymptomatic patients without anaemia or thrombocytopenia, urgent referral via the 2 week wait is **NOT** appropriate. These patients should be referred routinely to haemato-oncology.*

3 Investigation and Diagnosis

3.1 Diagnosis

The diagnosis of CLL/small lymphocytic leukaemia (SLL) is currently based on the combination of lymphocyte morphology, the presence of $>5 \times 10^9/L$ circulating clonal B-cells persisting for 3 months and a characteristic immunophenotype.

Morphologically, on bone marrow (BM) and peripheral blood smears, CLL cells appear as small lymphocytes with condensed 'cracked mud' clumped chromatin and scanty cytoplasm. Smear or smudge cells are typically observed in the PB. Atypical CLL usually shows less condensed nuclear chromatin and nuclear irregularities. Bone marrow trephine biopsies may show interstitial, nodular and/or diffuse infiltration, proliferation centres are less common in the BM than in lymph nodes. Enlarged lymph nodes show effacement of the architecture, with a pseudofollicular pattern of regularly distributed pale areas corresponding to proliferation centres containing larger cells in a dark background of small cells. If diagnosis of CLL / SLL is made on tissue biopsies or on bone marrow trephine biopsy, characteristic phenotype of CLL/SLL needs to be confirmed by immunohistochemistry. A panel including CD20, CD3, CD5, CD10, CD23, cyclin D1 and Ki67 is essential. Additional work-up that includes BCL6, BCL2, Lymphoid Enhancer Binding Factor 1 (LEF1), SOX11, MUM1 and CD38 may be value. LEF1 is particularly helpful. CLL/SLL cells characteristically express CD19, CD20, CD5, CD23, BCL2 and LEF1, and are negative for CD3, CD10 and SOX11. There may be weak expression of cyclin D1 in cells within the proliferation centres. MUM1 staining highlights proliferation centres.

On flow cytometry, CLL cells typically express CD5, CD19, CD23, weak monotypic surface immunoglobulin and weak or absent CD79B, CD22 and FMC7. A minimum recommended panel of monoclonal antibodies and scoring system for the diagnosis of CLL is shown below (Table 1). In addition, CD20, CD22, CD43, CD11c and CD10 should be included to aid in the differential diagnosis between CLL, atypical CLL, MCL and FL.

Table 1. A recommended minimum panel of monoclonal antibodies and scoring system for the diagnosis of CLL

Marker	Score 1	Score 0
Smlg	Weak	Strong
CD5	Positive	Negative
CD23	Positive	Negative
FMC7	Negative	Positive
CD22 or CD79B	Weak	Strong
Score >3 suggestive of CLL; score <3 suggestive of other B-cell malignancy		

Using this scoring system, 92% of CLL cases score 4 or 5, 6% score 3 and 2% score 1 or 2; all B-cell lymphomas score 1 or 2.

CD5 positivity is present in >90%. If CD5 negative, consider alternative diagnoses. Additional antigen targets for CLL diagnosis include CD43, CD160, CD200, CXCR5 and ROR-1, which also aid high sensitivity minimal residual disease (MRD) analysis.

The 2008 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues recognised monoclonal B-cell lymphocytosis (MBL) defined as the presence of monoclonal B-cell populations in the peripheral blood of up to $5 \times 10^9/L$ either with a phenotype of CLL, atypical CLL or non-CLL (CD5-), in the absence of other lymphomatous features. Despite approximately 12% of the healthy population demonstrating some MBL-like population, it is now widely accepted that MBL precedes virtually all cases of CLL/SLL. Patients with a clonal lymphocyte count between 3 and $5 \times 10^9/L$, in the absence of lymphadenopathy, splenomegaly or cytopenias, are classified as clinical monoclonal B-lymphocytosis with a risk of progression to CLL of 1–2% per year.

The proposed WHO revision will retain the current criteria for MBL, but will emphasise that “low-count” MBL, defined as a PB CLL count of $<0.5 \times 10^9/L$, must be distinguished from “high-count” MBL because low count MBL has significant differences from CLL, an extremely limited, if any, chance of progression, and, until new evidence is provided, does not require routine follow-up outside of standard medical care. In contrast, high count MBL requires routine/yearly follow-up, and has very similar phenotypic and genetic/molecular features as early stage CLL (Binet A / Rai stage 0), although immunoglobulin heavy chain variable region (IGHV)-mutated cases are more frequent in MBL. The proposed revision will also eliminate the option to diagnose CLL with $<5 \times 10^9/L$ PB CLL cells in the absence of extramedullary disease even if there are cytopenias or disease-related symptoms.

There is no current indication to screen family members for the presence of a circulating clonal B-cell population or for genetic susceptibility.

Table 2. Distinguishing between CLL, monoclonal B-cell lymphocytosis (MBL) and small lymphocytic lymphoma (SLL)

Criteria	CLL	MBL	SLL
Clonal B lymphocytes $>5 \times 10^9/L$	Y	N	N
Disease-related cytopenias	Y/N	N	Y/N
B symptoms	Y/N	N	Y/N
Lymphadenopathy and/or splenomegaly	Y/N	N	Y

3.2 Evaluation at presentation

The following should be undertaken:

- history of infections, B symptoms: weight loss and night sweats, unexplained fevers, severe lethargy
- family history of lymphoid malignancy
- performance status (PS)
- physical examination for lymphadenopathy/splenomegaly/hepatomegaly
- FBC + peripheral blood film (PBF)
- sample sent to the Haematological Malignancy Diagnostic Service (HMDS) for diagnostic immunophenotype.

Further tests performed at diagnosis include: direct antiglobulin test (DAT), reticulocyte count, biochemistry (including urate and lactate dehydrogenase (LDH)), serum immunoglobulins (Igs), paraprotein and $\beta 2$ -microglobulin (B2M), viral (hepatitis and HIV serology).

Bone marrow (BM) aspirate and trephine biopsy is not usually necessary at diagnosis but is indicated in cases with atypical features or to rule out other causes of anaemia/thrombocytopenia (e.g. auto-immune). Outside a clinical trial, pre-treatment BM is not usually required but post-treatment BM would be required to fully evaluate the response, and may be indicated in patients who have received treatment with the aim of achieving a complete response (CR).

CT scans are not routinely required for initial evaluation, but should be performed in cases of SLL.

Lymph node biopsy is only required if there is doubt about the diagnosis or if high-grade transformation is suspected.

3.3 Staging

Staging is based on clinical parameters and not on specialist investigations.

Two staging systems are widely used: Binet and Rai, which has been modified to reduce the number of prognostic groups from 5 to 3.

Table 3: Staging in CLL

BINET stage		Features
A		<3 lymphoid areas*
B		>3 lymphoid areas
C		Haemoglobin <100g/L or platelets <100 x 10 ⁹ /L

RAI stage	Risk group	
0	Low	Lymphocytosis only
I		Lymphadenopathy
II	Intermediate	Hepato or splenomegaly + lymphocytosis
III / IV	High	Haemoglobin <110g/L or platelets <100 x 10 ⁹ /L

* The five lymphoid areas comprise: uni or bilateral cervical, axillary and inguinal lymphoid, hepatomegaly and splenomegaly

For CLL, both Rai (0–IV) and Binet (A–C) stages need to be recorded and submitted to COSD to be considered ‘fully staged’.

3.4 Prognosis

The following factors affect prognosis:

- Patient-related:
 - Age, gender, PS, co-morbidities.
- Disease-related:
 - disease stage, lymphocyte doubling time (LDT), marrow failure, immunodeficiency/auto-immunity

- lymphomatous transformation
- genomic aberrations including deletions of 17p, 11q, 13q and trisomy 12 as determined by FISH or other means
- mutations in certain genes, for example NOTCH1, SFB31 and BIRC3
- complex karyotype, as determined by conventional cytogenetics or other means
- biomarkers including the mutational status of IGHV, CD38, ZAP70, B2M.
- Treatment-related:
 - type of treatment, response/toxicity, minimal residual disease (MRD) status.

Stage A patients who have Hb >10g/dl, lymphocytes <30 x 10⁹/L, minimal or no lymphadenopathy, non-diffuse pattern of BM involvement and an LDT of >12 months have an 80% chance of being alive at 10 years and only 15% are likely to require treatment.

With the exception of determining the status of the TP53 gene, it is not necessary to determine prognostic factors for treatment management.

Identifying a TP53 abnormality in patients with no clinical indication for therapy is not an indication for treatment; however, patients should always be screened for the presence of TP53 disruption (both deletion of 17p AND TP53 mutation analysis) prior to initial and subsequent treatment.

3.5 Minimal residual disease (MRD)

Recent evidence suggests that obtaining MRD after treatment (as determined by 6 or 8 colour flow in both bone marrow and peripheral blood samples) is an excellent predictor of outcome. However, outside of clinical trials, determination of MRD is not mandated.

4 Service Configuration Across London

All new and relapsing cases should be discussed at the local network multidisciplinary team (MDT) meeting. This should ensure consistency and quality of treatment from specialist expertise and access to the latest clinical trials. Each MDT meeting should be composed of the recognised quorate membership as dictated by the recent *Improving Outcomes* guidance for haematological malignancies.

All new diagnoses should be centrally reviewed by a specialist haematopathologist. Histopathology laboratories reporting lymphoma should have the facility to carry out immunohistochemistry using a basic panel of antibodies locally, with access within the network to a wider range of antibodies and to molecular techniques should they be required to evaluate complex cases. All laboratory methods, including immunohistochemistry and molecular technique, are subject to standard quality assurance systems.

The MDT referral form requires full patient details including NHS number, DOB, clinical history, presence of associated co-morbid illness and PS. The outcome reported requires the stage of the disease (Ann Arbor), classification, the histological diagnosis, ICD code and prognostic index score if appropriate. Details of the key worker should be recorded.

The MDT should recommend a management plan including treatment modality and response assessment details. The final decision should be signed off by the MDT lead or designated cover and communicated to the patient's GP within 24 hours, as well as the referring physician (if applicable).

5 Patient Information and Support

If the diagnosis of CLL or B-PLL is certain, patients should be informed that these are cancers of the blood, bone marrow and immune system. Most patients will not require treatment at the time of diagnosis. Their prognosis, which is very variable, should be discussed along with possible treatment options and clinical trials or research studies currently available, as appropriate.

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

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

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

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

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

www.macmillan.org.uk/Cancerinformation/Cancerinformation.aspx

Particularly important aspects of communication and patient information may include:

- treatment intent – whether the condition is curable/incurable
- the concept of watch and wait
- the range and types of therapy (including novel treatments and stem cell transplantation (SCT))
- clinical trials
- the fact that follow-up will be indefinite for chronic incurable disease
- fertility, if appropriate
- treatment toxicity and late effects
- available patient support groups, namely, CLLSA (www.clisupport.org.uk/).

6 Treatment

6.1 Principles

The first decision to be made in CLL is whether the patient requires therapy at the time of initial diagnosis. The disease shows extreme heterogeneity in its presentation and rate of progression, and there is no evidence that early treatment of asymptomatic or stable disease improves long-term survival.

Once a decision is made to give treatment, it is essential to know the status of the TP53 gene, as patients with TP53 disruption (either deletion of 17p or mutation of TP53) fare badly with chemo-immunotherapy and should be offered treatment with non-chemotherapy based regimens. Testing for 17p deletion is therefore mandatory (by FISH or other appropriate means), and if absent, testing for a TP53 mutation must be performed (by Sanger sequencing or other means).

Although not mandatory, testing the mutational status of the IGHV is highly desirable. Accumulating evidence indicates that patients with mutated IGHV respond well to all therapies including chemo-immunotherapy, and may have long durable remissions especially if they obtain MRD negativity. Patients with unmutated IGHV do not have durable responses to such therapy, regardless of initial response, whereas responses with targeted therapies including BTK inhibitors and Venetoclax appear to be similar at least in early follow up to the mutated group.

In patients with an intact TP53 pathway, the level of patient fitness must be determined as this influences the choice of chemo-immunotherapy. This will include an assessment of performance score, age and the presence or absence of co-morbidities.

6.1.1 Indications for first-line treatment

Treatment is offered as per the IWCLL 2008 criteria (summarised below). Otherwise, patients requiring no initial therapy should be monitored at appropriate intervals, watching for evidence of disease progression and/or complications (auto-immune, infection). Binet stage A patients generally do not need treatment. Stage A patients who develop auto-immune haemolytic anaemia (AIHA) or idiopathic thrombocytopenic purpura (ITP) in the absence of disease progression should be treated in the standard way for the auto-immune phenomenon but do not require cytoreductive therapy, unless this complication is refractory to standard treatment, e.g. with steroids.

Treatment is indicated in Binet stage A with progressive disease and Binet stage B, if there is:

- Worsening anaemia and/or thrombocytopenia not auto-immune
- lymphocyte doubling time (LDT) of <6 months
- lymphadenopathy (bulky, progressive or symptomatic)
- splenomegaly (massive, progressive or symptomatic)
- systemic symptoms (i.e. 10% unintentional weight loss, significant fatigue (ECOG PS 2 or worse), fevers of >38°C for 2 weeks without evidence for infection or night sweats for >1 month without evidence of infection)
- AIHA or ITP poorly responsive to standard therapy.

Treatment is generally indicated for patients with Binet stage C who by definition have anaemia and/or thrombocytopenia secondary to marrow infiltration.

- Hypogammaglobulinemia is not an indication for therapy.

6.2 First-line therapy

- CLL currently remains incurable even with newer agents, although in certain disease groups (for example patients with mutated IGHV who receive FCR and obtain an MRD negative remission), very long remissions (effectively cure) can be achieved. The durability of responses with novel agents remains unknown.
- The role of allogeneic transplantation remains undefined in the era of newer agents but should still be considered in selected cases of fit patients especially those with certain poor risk characteristics such as the presence of TP53 disruption, especially if in conjunction with other genomic aberrations. Discussion with a transplant centre with an interest in CLL is therefore advised.
- All patients should be considered for entry into available clinical studies.

6.2.1 Initial treatment for fit patients with no TP53 disruption

- FCR x 6 cycles (approved by NICE June 2009 TA 174) is the available treatment of choice for fit patients with no TP53 disruption (caution in patients with renal impairment).
- Bendamustine + rituximab would be an acceptable alternative for patients where FCR is contra-indicated.
- Ibrutinib (not NICE funded and no ongoing TA), shows improved progression free survival and less toxicity compared to both FCR and BR, especially in the IGHV unmutated IGHV group, but is unlikely to become available.

6.2.2 Initial treatment of less fit patients with no TP53 disruption

- Venetoclax Obinutuzumab (NICE TA ongoing) may become available and is likely to become the treatment of choice especially in the IGHV unmutated group
- In the absence of the above, Chlorambucil with obinutuzumab is indicated for less fit patients and both are NICE approved.
- Alternatively, bendamustine and rituximab can be considered.
- Chlorambucil with rituximab is not recommended.
- Chlorambucil monotherapy for very frail patients may be considered for those patients who cannot tolerate a monoclonal antibody.
- Ibrutinib (not currently NICE funded and no ongoing TA) shows improved PFS and less toxicity than Chlorambucil Obinutuzumab and would be a suitable alternative for less fit patients.

6.2.3 Initial treatment for patients with TP53 disruption

- A minority of patients (~5-10%) will have TP53 disruption at the time of first treatment. Patients with this abnormality have an inadequate response and outcome with standard chemo-immunotherapy (CIT) regimens and these should not be offered.

- B-cell receptor (BCR) pathway inhibitors have significant efficacy in this subset of patients. Ibrutinib is the treatment of choice for first-line treatment of patients with TP53 disruption. Idelalisib (given with rituximab) is only given in patients where ibrutinib is not suitable.
- These B-cell receptor (BCR) inhibitors are administered orally and generally have a favourable toxicity profile. However, specific side effects are seen with these agents which need to be managed and monitored, e.g. increased risk of atrial fibrillation with ibrutinib and increased risk of opportunistic infections (CMV, PJP) with idelalisib. Specific recommendations on the monitoring of idelalisib for colitis, transaminitis, neutropenia and opportunistic infections are available on the EMA and company website.
- Venetoclax is licensed for use in patients with TP53 disruption for whom BCR inhibitors are not suitable. Venetoclax, a BCL2 inhibitor results in a rapid reduction of disease at all sites and there is a high risk of tumour lysis syndrome (TLS). Patients can be risk stratified as low or high risk depending on the extent of adenopathy and the level of the WCC. Initial delivery of venetoclax should be done following a specific ramp up schedule and may initially require inpatient admission. Company guidelines are available as well as (see specific guidance on prevention and management of TLS).
- CR (complete remission): all the criteria have to be met, and patients have to lack disease-related constitutional symptoms; CRi is a category defined by failure to recover satisfactory counts but other criteria for CR are met; PR (partial remission): at least two of the criteria of group A plus one of the criteria of group B have to be met; SD is absence of PD and failure to achieve PR.

Table 4. Response assessment

Parameter	Group	CR*	PR	PD
Lymphadenopathy	A	None >1.5 cm	Decrease \geq 50%	Increase \geq 50%
Hepatomegaly	A	None	Decrease \geq 50%	Increase \geq 50%
Splenomegaly	A	None	Decrease \geq 50%	Increase \geq 50%
Blood lymphocytes	A	>4,000/ μ l	Decrease \geq 50% from baseline	Increase \geq 50% over baseline
Marrow	A	Normocellular, <30% lymphocytes, no B-lymphoid nodules	50% reduction in marrow infiltrate or B-lymphoid nodules	
Platelet count	B	>100.000/ μ l	>100.000/ μ l or increase \geq 50% over baseline	Decrease of \geq 50% from baseline secondary to CLL
Haemoglobin	B	>11.0g/dl	>11g/dl or increase \geq 50% over baseline	Decrease of >2g/dl from baseline secondary to CLL
Neutrophils	B	>1,500/ μ l	>1,500/ μ l or >50% improvement over baseline	

6.2.4 Maintenance therapy

- Despite evidence from randomised studies of benefit in PFS but not OS from anti-CD20 maintenance, this is not currently recommended in CLL.

6.3 Second-line and subsequent therapy

- As for first-line therapy, the indications as to which patients meet criteria for treatment remain as defined by the IWCLL 2008 guideline. Even after relapse, patients can be managed once again with a watch and wait strategy.
- At the time of re-treatment initiation (and any subsequent lines of therapy), pre-treatment assessment remains as for first-line therapy and must include testing for the presence or absence of TP53 disruption (deletion of 17p +/- TP53 mutation).
- Current NICE approved therapies include fixed duration (2 years) Venetoclax Rituximab, or indefinite Ibrutinib/ Idelalisib (given with Rituximab)
- The choice of Venetoclax Rituximab versus a BCR inhibitor will be determined by a number of disease and patient factors as there is no head to head comparison of VR with BCR inhibitors.
- All patients with TP53 disruption should receive either Venetoclax Rituximab or a BCR inhibitor and CIT is not indicated. Specific monitoring for each regimen is required
- In patients with an intact TP53 pathway, the same therapies should be offered. These patients would, however, be expected to respond to repeat CIT and this treatment could be considered in specific circumstances (e.g. a very good and durable response to first-line CIT)
- Venetoclax monotherapy can be used for patients who fail or who are intolerant of a BCR inhibitor. The same caveats exist for the risk of TLS as indicated above.
- Similarly, lack of response or intolerance to VR would indicate use of a BCR inhibitor
- HDMP +/- rituximab, rituximab alone, splenectomy and radiotherapy may all be considered as palliative therapy for late-stage refractory patients.
- All patients should be considered for appropriate relapsed/refractory clinical trials.

6.4 Allogeneic stem cell transplantation and cellular therapies

- In 2006, the European Group for Blood and Marrow Transplantation (EBMT) 2006 recommended that allogeneic transplantation is a reasonable option for fit patients with high-risk features: abnormalities of TP53 in first or subsequent remission; non-response or early relapse (within 12 months) after purine analogue-containing therapy; relapse within 24 months after purine analogue combination chemo-immunotherapy. Guidelines have now been updated in 2018 integrating newer therapies and disease/patient risk factors. **However, the current indications for transplant are unclear given the availability of effective options for all three of the EBMT categories.**
- Patients should be discussed/referred early to a local transplant centre with appropriate expertise.
- Autologous SCT is no longer recommended, except in cases of Richter's transformation, as an alternative to allo-SCT for consolidation after chemotherapy.

- CAR-T therapy is currently unavailable but is being explored in clinical trials

6.5 Fertility

Consideration of fertility preservation should be made for those of reproductive age (men below the age of 55 and women below the age of 40).

7 Management of Disease-related Complications and Treatment-related Complications

7.1 Disease-related complications

7.1.1 Auto-immune haemolytic anaemia or thrombocytopenia

- AIHA is reported in 10–20% of CLL patients, and ITP in 2–5%. Pure red cell aplasia (PRCA) and auto-immune neutropenia are rarer but probably under-recognised. Patients with underlying haemolysis should avoid fludarabine-containing regimens.
- AIHA or ITP should be treated before deciding whether therapy for CLL is needed. For more detailed information, see <https://b-s-h.org.uk/guidelines>.
- Patients with warm AIHA or ITP should be treated according to guidelines for idiopathic AIHA or ITP:
 - prednisolone at 1mg/kg body weight per day for 2–4 weeks, tapering off over several weeks.
 - for ITP, IV Ig 1g/kg as a single infusion (responses are transient) or 0.4/kg over 5 days can be used if immediate response is required (e.g. before surgery).
 - cyclosporin A or mycophenolate mofetil (MMF) may be indicated in resistant cases or to maintain response and allow withdrawal of steroids.
 - rituximab 375mg/m² weekly x 4–6 (some studies have used 100mg rituximab weekly with good effect) (may require prior agreement for funding).
 - combination therapy with rituximab, cyclophosphamide and dexamethasone can be used in resistant cases.
 - splenectomy.
 - avoid re-treatment with fludarabine in patients with a previous history of purine analogue-related AIHA or ITP.
 - TPO-R agonists (eltrombopag/romiplostim) can be helpful in resistant ITP.

7.1.2 Infection

- Infective complications are a common clinical problem and account for the majority of CLL deaths.
- Susceptibility is multifactorial and due to the disease itself, or as a result of therapy, and includes hypogammaglobulinemia, neutropenia, impaired T and natural killer cell function and defective complement activity.
- Most infections are bacterial, but fungal, viral and opportunistic infections are increasingly prevalent with newer treatments (purine analogues, alemtuzumab and methylprednisolone).
- All patients should receive vaccination against encapsulated bacteria (pneumococcus, HIB) and annual influenza, but NOT live vaccinations (including the current shingles vaccine). Advice on the use of specific vaccines is available at www.gov.uk/government/collections/immunisation.

- Patients presenting with infection or unexplained PUO, even in the absence of neutropenia, should routinely have a full sepsis screen including viral swabs and PCR for Epstein–Barr virus (EBV), cytomegalovirus (CMV) and adenovirus.
- All infections should be treated vigorously, especially in those patients receiving treatment and/or with a prior history. Patients should be told to contact their doctor or the clinical nurse specialist at the first sign of infection for advice.

7.1.3 Secondary hypogammaglobulinaemia

- Up to 70% of patients with CLL have hypogammaglobulinemia and IV Ig (0.5g/kg every 3–4 weeks) is recommended for those with recurrent severe infections despite prophylactic antibiotics. Monitor IgG levels and maintain trough IgG level in the normal range.
- Referral to appropriate specialist teams for subcutaneous home administration should also be considered.

7.2 Treatment-related complications

7.2.1 Febrile neutropenia

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

Patients with neutropenic pyrexia or sepsis should be treated according to local protocols for neutropenic sepsis (and following National Institute for Health and Care Excellence (NICE) guidance).

In addition, for haemato-oncology patients the following are mandatory:

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

Such patients should ideally be cared for by specially trained nurses on a BCSH Level 2b-3 unit. The use of G-CSF is highly dependent upon the context of the disease and the chemotherapy protocol in which it is being used. G-CSF is used to hasten recovery of the neutrophil count, decrease risk of infection and reduce hospital stay. However, evidence supporting improved survival with G-CSF is lacking.

7.2.2 Management of specific adverse effects related to ibrutinib

There are a number of considerations specifically relating to the use of ibrutinib including interaction with CYP3A4 inhibitors, increased bleeding risk that can be exacerbated by concomitant anti-platelet/anti-coagulant therapy, atrial fibrillation, ventricular tachyarrhythmias and hypertension.

- Concomitant use of ibrutinib with strong or moderate CYP3A4 inhibitors should be avoided wherever possible. If concomitant treatment with a CYP3A4 inhibitor is required consideration should be given to reducing the dose of ibrutinib to 140 mg daily. A list of commonly used strong and moderate CYP3A4 inhibitors can be found in Gribben *et al.* 2018.
- For patients already on Vitamin K antagonists who require ibrutinib, bleeding risk may be reduced by changing to a direct oral anticoagulant and considering dose reduction if risk benefit:ratio allows.
- For patients on dual anti-platelet therapy (e.g. post-stenting), withdrawal of one of these agents should be considered in consultation with the cardiologist. Single anti-platelet therapy can be continued but consider stopping this if there is excessive bruising or bleeding.
- For major surgical or invasive procedures, ibrutinib should be stopped for at least 7 days prior to the intervention and not be restarted for at least 7 days after the procedure. Similarly, for emergency surgical procedures ibrutinib should be withheld for at least 7 days or until the surgical site is reasonably healed. For minor procedures (e.g. central line placement, needle biopsy) ibrutinib should be stopped at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For investigational procedures (e.g. endoscopy) ibrutinib should be stopped 3 or 7 days before the procedure and not be restarted for at least 3 or 7 days after, depending on the extent of any biopsies or instrumentation.
- Due to the occurrence of hypertension, atrial fibrillation and ventricular tachyarrhythmia in patients on ibrutinib, all patients should be closely monitored for cardiac symptoms. An alternative agent should be considered in patients with a significant cardiac history.
- In the event of atrial fibrillation (AF), ibrutinib should either be continued or withheld depending on AF severity. While ibrutinib can be continued in patients with asymptomatic/mild AF, it should be temporarily withheld for grade ≥ 3 AF. In these patients, ibrutinib can be re-started as soon as AF is stabilised after evaluation of the risk:benefit ratio. Patients should be managed with the advice of a cardiologist.
- Blood pressure should be monitored during ibrutinib therapy. If a patient experiences hypertension or worsening hypertension attributable to ibrutinib therapy, this should be vigorously treated to minimise the risk of further complications such as AF.

8 Supportive Care

Regular prophylactic antibiotics or IV Ig should be considered for patients with recurrent serious infections (as per national guidelines for immunoglobulin usage).

8.1 Infection prophylaxis

- All patients should receive vaccination against encapsulated bacteria (pneumococcus, HIB) and annual influenza but NOT live vaccinations (including the current shingles vaccine).

Advice on the use of specific vaccines is available at www.gov.uk/government/collections/immunisation.

- Patients receiving purine-analogue containing chemotherapy will usually receive PJP and herpes prophylaxis. In addition, those patients receiving high-dose steroids should also have anti-fungal prophylaxis, and those receiving alemtuzumab require weekly monitoring for CMV reactivation.
- Patients on idelalisib should receive PJP and herpes prophylaxis. Regular monitoring of CMV is advised.
- At the present time, there is no consensus on prophylaxis for ibrutinib treatment but cases of PJP and other opportunistic infections have been described.
- The use of granulocyte-colony stimulating factor (G-CSF) should be considered in patients with prolonged/severe neutropenia post-chemotherapy.
- Patients receiving monoclonal antibodies such as rituximab should be tested for Hepatitis A,B and C (also possibly E) for evidence of prior infection. Those at risk of reactivation should receive appropriate prophylaxis during treatment (refer to specific guidance and liaise with hepatologist).

8.2 Transfusions

- Transfusion triggers should be chosen in advance for patients, depending on co-morbidities. For patients with no co-morbidities or bleeding risk, and in those who do not lead active lifestyles, it would be reasonable to aim for a target Hb >80g/dL.
- Patients treated with bendamustine, purine analogues (such as fludarabine) and alemtuzumab have a life-long requirement to receive irradiated cellular blood products if such transfusions are ever required. This should be registered in the local Trust blood bank and the patient should be given appropriate information and an alert card in case they are admitted to another hospital.

Patients should be counselled and empowered to “check and challenge” regarding blood products if required and be provided with the NHSBT information booklet and wallet card, while the sticker is placed on their casenotes.

Local and national policies and procedures regarding the notification, need for and administration of irradiated blood products should be followed when patients have received these agents or haematopoietic stem cell transplantation.

9 Treatment Summary and Care Plan

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

Treatment summaries should be agreed either when treatment ends or when there are any significant changes in treatment and follow-up plans. HNAs should be offered through follow-up, with a care plan completed to document the plans to address the issues raised by the patient, and an end-of-treatment HNA should be completed.

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

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

Recommendation

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

Patients who remain untreated on watch and wait follow-up should aim to have an annual HNA with an associated care plan agreed.

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

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

10 Follow-up Arrangements

- 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 pace of change.
- Patients established on oral targeted therapies will need to be seen for assessment of response, tolerability to the medications and repeat prescriptions. Intervals of 12 weeks in common for this.
- Patients on follow-up after completion of treatment should be seen as clinically appropriate, reverting to the same schedule as stable stage A disease if no sign of recurrent disease.
- Remote systems (Telemedicine) for follow-up of patients should be considered, with several options in existence and evidence of high levels of patient satisfaction.

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

Surveillance imaging is not recommended.

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

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

11 Research and Clinical Trials

Where possible, all eligible patients should be entered into an appropriate clinical trial. Consideration should be given to referring a patient to a specialist centre where a suitable trial may be open.

Bio-banking of diagnostic material may be considered if appropriate approvals (ethics/R&D permission) are in place at the referring site. Alternatively, patients can be referred directly.

12 End-of-life Care

Discussions about prognosis and treatment should also include discussions of end-of-life care, to facilitate transitions between active disease-modifying therapy to clinical trials, or supportive care only at the time of disease progression/non-response. Full integration with palliative care services should be seamless and end-of-life treatment decisions discussed with patients and their families

where appropriate, fully respecting the dignity of patients and the sensitivities of traumatic, difficult situations.

The named clinical nurse specialist/key worker, patient, family members and palliative care teams as well as members of the inpatient ward team may be involved. Clear documentation of the discussion with guidance to the treating teams is helpful in communicating these discussions and outputs to the wider team that may care for the individual.

13 Specific/Miscellaneous Considerations

13.1 Richter's transformation

- Richter's transformation occurs when a patient with CLL then develops a diffuse large B cell lymphoma (or very rarely a classic Hodgkin lymphoma). Laboratory tests show that in about half the cases the lymphoma arises from the same population of cells as the leukaemia and otherwise is clonally unrelated when the outcome is more consistent with that of *de novo* diffuse large B-cell lymphoma (DLBCL).
- It occurs in about 10% patients with CLL and usually has rapid progression in a single nodal site accompanied by a rise in LDH.
- May also undergo transformation in BM, central nervous system or organs (e.g. liver, kidneys).
- It is very important to consider this possibility and arrange appropriate biopsy to confirm. Use of PET scan in this situation can assist in directing the best site for tissue biopsy (i.e. where there is high uptake SUV).

Treatment options include:

- CHOP-type regimen + rituximab
- platinum-based regimen +/- rituximab.

Choice is dependent on previous treatment, the general fitness of the patient, etc., and should be decided on an individual basis.

All eligible patients should then proceed to autologous or allogeneic HSCT.

13.2 B-PLL

- B-PLL is a very rare aggressive leukaemia with poor survival. Morphology and immunophenotype are distinct from CLL. Signs and symptoms are a very high white blood cell count and massive splenomegaly but minimal lymphadenopathy.
- TP53 deletion/mutation in up to 50% of cases.
- Assessment and management are as for CLL.
- Induction treatment with FCR or BR if no TP53 deletion, BCR inhibitor if TP53 abnormality.
- Consider consolidation with allogeneic SCT in eligible patients.
- Splenectomy may be beneficial in resistant cases.
- Supportive care is as for CLL.

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5th Floor Alliance House
12 Caxton Street
London SW1H 0QS