PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

LYMPHOMA

CHRONIC LYMPHOCYTIC LEUKEMIA

Site Group: Lymphoma – CLL

Date guideline created: July 2023

1. Introduction

Chronic lymphocytic leukemia (CLL) is a common indolent lymphoma affecting mainly older adults. This guideline relates to the management of CLL currently at the Princess Margaret Cancer Centre. This guideline does not address the management of T-prolymphocytic leukemia or Richter's transformation.

2. Prevention

Prevention strategies are not currently available for CLL.

3. Screening and Early Detection

Screening and early detection do not play a role in the diagnosis and management of CLL. While monoclonal B-cell lymphocytosis with CLL-immunophenotype (MBL) is known to be a precursor condition to CLL, there are no early intervention strategies for patients with MBL.

In terms of incidental early detection of MBL, patients diagnosed with MBL with typical CLL-immunophenotype can be divided into low count MBL (LC-MBL, $<0.5x10^9$/L clonal B-cells on peripheral blood flow cytometry) and high count MBL (HC-MBL, $0.5\text{-}4.9x10^9$/L clonal B-cells). Patients with LC-MBL rarely progress to CLL and do not require any special follow up regarding this condition. Patients with HC-MBL should be counselled on the 1% risk per year of progressing to CLL requiring therapy, and that they have an increased risk for infection and secondary malignancy similar to patients with CLL (see Section 7). Occasionally, patients are incidentally diagnosed with CLL infiltration on lymph node biopsies done for other causes, who otherwise would be diagnosed with MBL based on peripheral blood. There are limited data that patients with MBL and lymph nodes <1.5cm have a similar low risk of progression to CLL compared to patients with MBL without lymphadenopathy. Thus, it is reasonable to classify such patients as nodal MBL, while patients with lymph nodes $\geq$1.5cm should be classified as CLL/SLL.

As HC-MBL is a benign condition, patients do not require specialized follow up at Princess Margaret Cancer Centre and can be discharged to follow up with their family physician on a yearly basis with routine bloodwork and physical exam. They should be advised to be referred back in the setting of any of the following symptoms: enlarging lymph nodes, symptomatic splenomegaly typically presenting with early satiety or left upper quadrant discomfort, cytopenias not explained by other causes (HGB <110, PLT <100), constitutional symptoms of drenching sweats, fevers without explanation or significant unintentional weight loss, fatigue limiting function without other causes, or any organ dysfunction felt to be related to lymphoma. There is no particular lymphocyte count that requires that patients be referred back for follow-up with a hematologist, but an arbitrary number of a lymphocyte count of $\geq 30x10^9$/L can be used to determine when patients should be referred back.

Patients diagnosed with MBL with atypical or non-CLL immunophenotype should be worked up for an underlying diagnosis of indolent lymphoma (refer to indolent lymphoma guidelines), and should be followed by a hematologist given limited data regarding risk of progression to symptomatic lymphoma.

4. Diagnosis

The diagnosis of CLL is dependent on immunophenotypic findings on flow cytometry, and/or histologic assessment of a surgically acquired incisional or excisional biopsy of an involved lymph node or other extra-nodal tissue, to ensure adequate evaluation based on morphology, immunohistochemistry and flow cytometry for accurate sub-typing. Bone marrow aspiration and biopsy can be considered as part of workup, and on rare occasions represent the primary biopsy site for final diagnosis.

5. Pathology

Patients are treated based on a diagnosis conforming to those described according to the 5th edition of the World Health Organization Classification of Haematolymphoid Tumours (WHO-HEAM5) and/or the International Consensus Classification (ICC), often after primary evaluation or pathology review by an expert Hematopathologist at the University Health Network. The immunophenotype is determined either immunohistochemistry on tissue with a panel consisting of CD5, CD20, CD23, LEF1, IGK and IGL, or, preferentially, by flow cytometry with a panel consisting of CD5, CD19, CD20, CD23, CD43, CD79b, CD81, CD200, IGK, IGL. These panels may be expanded to exclude other small B-cell lymphoma types. In order to make a diagnosis of CLL (over MBL), $\geq 5 \times 10^6$/L clonal B-cells must be measured on peripheral blood by flow cytometry.

Notably, the WHO-HAEM5 classification no longer considers B-PLL a separate disease entity. Prolymphocytic progression of CLL/SLL, defined by the presence of >15% prolymphocytes in the peripheral blood and/or bone marrow, is generally treated as high risk CLL.

6. Management

Patients who do not require treatment upfront:

Clinical staging criteria based on the Binet and/or Rai staging systems are used. Asymptomatic patients do not require staging with CT and/or PET scan. Among patients who do not meet iwCLL criteria for treatment, monitoring should occur every 3-12 months based on symptoms and tempo of disease. Per international guidelines, IGHV mutational status, FISH, and/or TP53 or other mutational testing is not performed until patients require treatment.

Pre-treatment evaluation and staging:

Staging Investigations:

When patients meet criteria for treatment, pre-treatment evaluation should include:

- Full history and physical examination including performance status
- CBC, albumin, LDH, beta-2 microglobulin, liver testing (bilirubin, ALT, AST, ALP), creatinine, immunoglobulin quantitation and serum protein electrophoresis (SPEP), direct antiglobulin test (DAT), haptoglobin

- HBsAg, HBsAb, HBcoreAb; HCV antibody and/or HIV testing can be considered

- CT head and neck, thorax, abdomen, pelvis is not generally required outside of risk-stratifying patients for venetoclax-based treatment

- FDG-PET scan should be performed on patients with suspicion for Richter's transformation, due to signs or symptoms such as rapidly growing lymphadenopathy, high LDH, or significant constitutional symptoms

- IGHV mutational testing, FISH for cytogenetics and/or assessment of genomic complexity (by karyotyping or optical genome mapping) if available, and molecular testing for TP53 and/or other recurrently mutated genes in CLL should be performed prior to treatment. UHN offers testing for recurrently mutated genes in CLL, though at the time of guideline writing, only TP53 mutation affects upfront management. Similarly, in terms of FISH or genomic complexity testing, the only chromosomal aberration which currently affects upfront treatment is 17p deletion.

- BM aspirate and biopsy with assessment of morphology, immunohistochemistry, flow cytometry, FISH, karyotype and/or molecular testing can be considered for patients with unexplained cytopenias

- 2D echocardiogram, baseline ECG, and/or Holter monitor for patients for whom BTK inhibitors are being considered who are known to have cardiac disease or with risk factors for cardiac disease

- Review of Pathology by UHN hematopathology

- Calculation of CLL-IPI score

Systemic therapy

- Enrolment to clinical trials is strongly encouraged.
- Treatments mentioned in this section are Health Canada approved for CLL. If not funded, this is clarified in parentheses.
- Preferred frontline treatment is dependent upon patient age, fitness, comorbidities, IGHV mutational status, FISH and/or karyotype, and molecular testing. Patient preferences for time-limited vs. continuous duration therapy must also be considered.
- Among young (<65 years), fit patients with mutated IGHV, and no evidence of 11q deletion, 17p deletion, or TP53 mutation, fludarabine/cyclophosphamide/rituximab therapy represents an effective and time-limited strategy with a potential for long term remissions in approximately 50% of patients. Alternative treatment options in this favourable risk group of patients include venetoclax-obinutuzumab (not currently funded in Ontario for this group of patients), ibrutinib-venetoclax (not currently funded in Ontario), or BTK inhibitors (not currently funded in Ontario for this group of patients).
- Among older or less fit patients with no 17p deletion or TP53 mutation, venetoclax-obinutuzumab (funded in Ontario if CIRS score >6 or eGFR <70ml/min) represents an effective, time-limited strategy with median progression free survival of 76.2 months in recently reported

6-year follow up data. Alternative approaches are the use of ibrutinib-venetoclax (not currently funded in Ontario), or the use of BTK inhibitors acalabrutinib (funded only if IGHV unmutated) +/- obinutuzumab (not currently funded in Ontario), or zanubrutinib (not currently funded in Ontario). These strategies have not been compared head to head. Caution should be undertaken in the use of ibrutinib-venetoclax in older patients with significant comorbidities, given the risk of treatment related mortality associated with this strategy in such patients in the GLOW trial.

- Among patients of any age with 17p deletion or TP53 mutation, a BTK inhibitor strategy with acalabrutinib or zanubrutinib (not currently funded in Ontario) is the preferred treatment option, with median progression free survival of 76% at 48 months or 79% at 42 months in follow-up of the ELEVATE-TN or SEQUOIA trials, respectively. However, if there is patient or clinician preference for time-limited therapy and/or comorbidities where avoidance of BTK inhibitors is preferable, venetoclax-obinutuzumab is a reasonable treatment strategy also, with median progression free survival of 51 months in 6-year follow up of the CLL14 trial, or ibrutinib-venetoclax (not currently funded in Ontario) which was studied in younger patients with 17pdel and/or TP53 aberration in the Phase II CAPTIVATE trial, where exploratory analyses described a 4-year PFS of 63% (95% CI, 41–79).
- Ibrutinib is not considered a preferred single-agent BTK inhibitor in the frontline or relapsed/refractory setting due to head-to-head randomized trials showing equivalent or superior efficacy of second generation BTK inhibitors with an improved safety profile

Re-Staging Investigations:

- History and physical examination; including adverse events and performance status.
- Complete blood count
- Repeat of imaging tests previously demonstrating involvement by CLL is not generally indicated in clinical practice, unless documentation of response to treatment is required/desirable
- Bone marrow biopsy if involved and documentation of complete response to treatment is required/desirable.

Minimal Residual Disease testing

- After completion of time-limited therapy, minimal residual disease (MRD) testing via peripheral blood and/or bone marrow can be considered for prognostic purposes, though at this time, MRD testing does not change management. MRD testing appears to have less prognostic value in patients treated with ibrutinib-venetoclax combination therapy.
- Serial MRD testing is generally not advised outside of a clinical trial setting
- MRD testing is not recommended for patients on continuous BTK inhibitor therapy

RELAPSED/REFRACTORY DISEASE

General approach:

- The following should be considered in patients who have progression/relapse:
  - Risk status of the disease including development of genome complexity (assessed by karyotype or optical genome mapping) if available, development of 17pdel or TP53 mutation if not previously present, development of resistance mutations for targeted therapies such as BTK or BCL2 mutations if available.
  - Whether there are any features concerning for Richter's transformation such as constitutional symptoms, rapidly progressive lymphadenopathy, unusual extranodal sites of disease, or

markedly elevated LDH
    - Optimization of vaccination status and comorbidities as preparation for treatment
- If patients are on continuous therapy at time of progression, therapy should be continued to prevent disease flare. Therapy should also be overlapped with the next line of therapy, including allogeneic stem cell transplant, except in circumstances where there is overlap of toxicities (e.g. BTK inhibitor to non-covalent BTK inhibitor) or interactions (e.g. idelalisib to venetoclax)
- In the absence of traditional iwCLL treatment criteria, determining the best time to start the next line of therapy is based on a combination of factors, including the risk status of the disease, fitness of the patient, tempo of progression, and planned next line of therapy

Treatment options:
- Enrollment into clinical trials is strongly encouraged
- In general, patients should not be re-treated with a chemo-immunotherapy based regimen based on the poor progression-free survival associated with retreatment in this circumstance
- Standard of care options include venetoclax-rituximab combination therapy, venetoclax monotherapy, and continuous therapy with BTK inhibitors. These therapies have not been compared head to head.
- In patients who received time-limited novel-therapy based regimens, re-treatment can be considered if a 12-month treatment-free interval has passed (funded in Ontario)
- Class-switch from BTK inhibitor to BCL2 therapy, or vice versa, can be considered
- In patients who previously discontinued BTK inhibitors for intolerance, retreatment with an alternate BTK inhibitor can be considered. However, if treatment was discontinued due to spontaneous intracerebral hemorrhage, or other severe toxicities such as serious cardiac arrhythmia, BTK inhibitor re-treatment is generally not advised.
- In fit patients of any age who are starting their second novel therapy class, assessment regarding the role of allogeneic stem cell transplant is recommended
- As above, ibrutinib is not considered a preferred single-agent BTK inhibitor in the relapsed/refractory setting due to head-to-head randomized trials showing equivalent or superior efficacy of second generation BTK inhibitors with an improved safety profile

6.1 Surgery

Surgery does not play a role in the primary management of patients with CLL, beyond the need for an adequate excisional biopsy for accurate diagnosis.

6.2 Chemotherapy

The role of chemotherapy in primary management of CLL is described above.

6.3 Radiation Therapy

Radiation does not generally play a role in the treatment of CLL.

6.4 Oncology Nursing

Refer to general oncology nursing practices

7. Supportive Care

7.1 Patient Education

Refer to general patient education practices

Patients should be educated on the increased risk of infection associated with CLL. They should be counselled on the value of primary prophylaxis with vaccination (particularly against COVID-19, influenza, pneumococcal infection, and shingles), role of secondary prophylaxis in the setting of severe and recurrent infections if hypogammaglobulinemia is present. Patients should also be counselled on the increased risk of secondary primary malignancies, particularly non-melanoma skin cancers, and the importance of routine second cancer screening described below.

Patients should be counselled that first degree relatives have a 5-7 times increased lifetime risk of CLL, however given the lifetime incidence of 0.6% in the general population, this is not a significant personal risk, and family members do not need special screening or testing for CLL, but rather should have a family physician and undergo routine follow up per Canadian guidelines. PMH does have a Familial Cancer Clinic. Guidelines to refer to this clinic relevant to patients with CLL include the following:

- Patients with a first degree relative who also has a diagnosis of CLL
- Patients with two close relatives with any lymphoid malignancy, myeloid malignancy, or bone marrow failure (includes aplastic anemia or prolonged unexplained pancytopenia)
- Patients with a personal history of at least two additional cancers

For patients on treatment, they should be counselled on the risk of interactions between novel therapies such as venetoclax or BTK inhibitors and other medications. They should be counselled on periprocedural considerations when on BTK inhibitors.

7.2 Psychosocial Care

Refer to general psychosocial oncology care guidelines

7.3 Symptom Management

Refer to general symptom management care guidelines

7.4 Clinical Nutrition

Refer to general clinical nutrition care guidelines

7.5 Palliative Care

Refer to general oncology palliative care guidelines

8. Follow-up Care

Monitoring

- Document physical examination of previously involved areas., and if desired, CT scanning to document response.

- At each subsequent visit:

- Document history and physical examination, toxicities, performance status; follow blood counts and other biochemistries

- Patients should be followed indefinitely given the lifetime risk of recurrence

- Counselling regarding physical and psychological health issues, including impact of treatment on quality of life, management of fatigue, fertility and contraception, cardiovascular fitness, risk of recurrence, and risk of second malignancy. Smoking cessation for smokers.

Oncology Clinic Follow-up Frequency:

First year	-	Visits every 3 months
2 - 3 years	-	Visits every 4 months
4 - 5 years	-	Visits every 6 months
> 5 years	-	annual follow up

Second malignancy screening

Routine primary care follow-up. In addition to recommended cancer screening based on national and provincial guidelines given the increased incidence of second malignancies in patients with CLL, yearly skin assessment by the family physician or a dermatologist is recommended given the enrichment for non-melanoma skin cancers as well.

9. References

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