Approaches in Hematology

Hematology Made Easy

Chronic Lymphocytic Leukemia

✓ **Chronic Lymphocytic Leukemia (CLL):** is an indolent disease characterized by clonal malignancy of mature B-cells.

✓ **Epidemiology:**
- Most common leukemia in the Western world.
- Mainly older patients; median age 70 years.
- M>F

✓ **Pathophysiology:** accumulation of neoplastic lymphocytes in blood, BM, lymph nodes, and spleen.

✓ **Clinical picture:**

1. 25% asymptomatic (incidental finding): Found by routine check-up as CBC.
2. 5-10% present with B-symptoms ≥1 of the following:
   - Unintentional weight loss ≥10% of body weight within the previous 6 months.
   - Temperature >38ºC,
   - Night sweats for ≥2 weeks without evidence of infection), extreme fatigue
3. Lymphadenopathy (50-90%), splenomegaly (25-55%), hepatomegaly (15-25%)
4. Immune dysregulation: autoimmune hemolytic anemia (DAT positive), ITP, hypogammaglobulinemia ± neutropenia.
5. BM failure: late, secondary to marrow involvement by CLL cells.

✓ **Investigation:**
- CBC: clonal population of B lymphocytes >5 x 10^9/L (> 5000)
- peripheral blood film
  - Lymphocytes are small and mature
  - Smudge cells: pathognomonic for CLL
- Flow cytometry characteristics of peripheral blood for the following:CD5, CD20dim, CD23, CD19.
- Cytogenetics: FISH (dictates response to therapy and prognosis).
- Imaging must be done post-therapy to Ensure post-treatment remission.
- BM aspiration: infiltration of marrow by lymphocytes in 4 patterns: nodular (10%), interstitial (30%), diffuse (35%, Worse prognosis), or mixed (25%).

- Staging: By Rai and Binet classification

Table 18.4 Staging of chronic lymphocytic leukaemia (CLL).

(a) Rai classification

Stage	
0	Absolute lymphocytosis >15 × 10^9/L*
I	As stage 0 + enlarged lymph nodes (adenopathy)
II	As stage 0 + enlarged liver and/or spleen ± adenopathy
III	As stage 0 + anaemia (Hb <10.0 g/dL)* ± adenopathy ± organomegaly
IV	As stage 0 + thrombocytopenia (platelets <100 × 10^9/L)* ± adenopathy ± organomegaly

(b) International Working Party classification

Stage	*Organ enlargement**	*Haemoglobin† (g/dL)*	*Platelets† (× 10^9/L)*
A (50–60%)	0, 1 or 2 areas		
B (30%)	3, 4 or 5 areas	≥10	≥100
C (<20%)	Not considered	<10	and/or <100

*One area = lymph nodes >1 cm in neck, axillae, groins or spleen, or liver enlargement.
†Secondary causes of anaemia (e.g. iron deficiency) or autoimmune haemolytic anaemia or autoimmune thrombocytopenia must be treated before staging.
Source: (b) Binet J.L. *et al.* (1981) *Cancer* **48**, 198.

✓ **Differential diagnosis**

- ❖ mantle cell lymphoma (MCL): These tumor cells express B-cell surface antigens and also express CD5, but usually not CD23. For cases that express CD23, staining for cyclin D1 or SOX11 and fluorescence in Situ hybridization (FISH) for detecting a translocation (11;14) are useful for establishing the diagnosis of MCL.

- ❖ Small lymphocytic lymphoma (SLL): In the World Health Organization classification, small lymphocytic lymphoma (SLL) and CLL are considered to be a single entity. The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with a number of B lymphocytes in the peripheral blood not exceeding 5 × 109/l. SLL cells show the same immunophenotype as CLL. The diagnosis of SLL should be confirmed by histopathological evaluation of a lymph node Biopsy, whenever possible.

- ❖ Monoclonal B-lymphocytosis' (MBL): In the absence of lymphadenopathy, organomegaly, cytopenia, or clinical symptoms, the presence of fewer than 5000 monoclonal B lymphocytes/μl defines 'monoclonal B-Lymphocytosis' (MBL) can be detected in 5% of subjects with normal blood count. Progression to CLL occurs in 1%–2% of MBL cases per year.

✓ **Natural History**

- Natural history: indolent and incurable; most cases show slow progression.
- Small minority present with aggressive disease; usually associated with chromosomal abnormalities (e.g., P53 deletion).

✓ Indications for treatment

1) Progressive marrow failure: The development or worsening of anaemia and/or Thrombocytopenia.
2) Massive (>10 cm) or progressive lymphadenopathy
3) Massive (>6 cm) or progressive splenomegaly
4) Progressive lymphocytosis: > 50% increase over 2 months or lymphocyte doubling time <6 months.
5) Systemic symptoms:
   - Weight loss > 10% in previous 6 months,
   - Fever >38 C for > 2 weeks,
   - Extreme fatigue,
   - Night sweats
6) Autoimmune cytopenias e.g., ITP

✓ Treatment

- First-line therapy is dictated by cytogenetic status and patient co-morbidities. Observation if early, stable, asymptomatic
- treatment options vary by region:
  - ℛ Commonly Fludarabine + Cyclophosphamide + Rituximab (FCR) in fit patients age <65, with normal creatinine clearance and lack of 17p deletion/p53 disease.
  - ℛ Chlorambucil (or Venetoclax + Obinutuzumab in the elderly).
  - ℛ Ibrutinib or Acalabrutinib in patients with unmutated IgVH and/or 17p deletion/p53 positivity
  - ℛ Corticosteroids and Rituximab in patients with autoimmune phenomena.
  - ℛ Radiotherapy for isolated bulky nodes

- Molecular therapies
  - Idelalisib – PI3K inhibitor
  - Ibrutinib, Acalabrutinib – BTK (Bruton's tyrosine kinase) inhibitor
  - Venetoclax – Bcl-2 inhibitor

✓ Guidelines

- Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia (CLL) have been issued by the following organizations:
  - National Comprehensive Cancer Network (NCCN)
  - International Workshop on Chronic Lymphocytic Leukemia (iwCLL)
  - European Society of Medical Oncology (ESMO)

- Diagnosis and Staging
  - All three guidelines are in agreement that the diagnosis of CLL requires the presence of ≥5 × 109/L B-lymphocytes in the peripheral blood and the clonality of the circulating B lymphocytes should be confirmed by flow cytometry.

  - The iwCLL guidelines also require persistence of lymphocytosis for longer than 3 months, while NCCN and ESMO do not.

- For adequate immunophenotyping to establish diagnosis by flow cytometry, the NCCN recommends using the cell surface markers kappa/lambda, CD19, CD20, CD5, CD23, and CD10. If flow cytometry is used to establish the diagnosis, cytospin for cyclin D1 or fluorescence in situ hybridization (FISH) for t(11;14); t(11q;v) should also be included.

- The NCCN recommends proceeding with lymph node biopsy if the diagnosis is not established by flow cytometry. Diagnosis on lymph node biopsy requires immunophenotyping of CD3, CD5, CD10, CD20, CD23, and cyclin D1.

- ESMO guidelines note that leukemia cells are characteristically small, mature-appearing lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernible nucleoli and having partially aggregated chromatin. Larger, atypical lymphocytes or prolymphocytes cannot exceed 55%.

- The IwCLL guidelines also allow for the diagnosis of CLL in the presence of cytopenia caused by clonal bone marrow involvement regardless of the peripheral B-lymphocyte count.

- Additional tests recommended prior to initiation of treatment include:
    i. Fluorescence in situ hybridization (FISH) to detect cytogenetic abnormalities, in particular deletion of chromosome 17 [del(17p)], 13[del(13q)] and 11 [del(11q)] and trisomy of chromosome12.
    ii. Molecular analysis to detect IGHV mutation status.
    iii. Determination of CD38 and ZAP-70 expression by flow cytometry or immunohistochemistry.
    iv. TP53 sequencing.
    v. Prior to chemoimmunotherapy, alemtuzumab or allogeneic stem cell transplantation, testing for hepatitis B and C viruses, cytomegalovirus (CMV), and human immunodeficiency virus (HIV)
    vi. Unilateral bone marrow aspirate and biopsy; however, some oncologists in the United States do not consider bone marrow analysis to be required.

- The NCCN considers the following essential in the workup of patients diagnosed with CLL:
    i. Physical examination with attention to node-bearing areas, including Waldeyer ring, and measurement of the size of liver and spleen.
    ii. Performance status determination.
    iii. Assessment of B symptoms.
    iv. Complete blood count and comprehensive metabolic panel.

- Treatment: The guidelines are in agreement that patients with early-stage CLL should not be treated with chemotherapy until they become symptomatic or display evidence of rapid progression of disease.Patients at low risk and intermediate risk (ie, Rai stages 0-II) who have no indications for treatment should be observed. Blood cell counts and clinical examinations should be performed every 3–12 months. Indications for treatment include the following:
  - Significant disease-related symptoms (e.g., fatigue, night sweats, weight loss, fever without infection)
  - Threatened end-organ function
  - Progressive bulky disease
  - Progressive anemia or thrombocytopenia
  - Progressive lymphocytosis

- Therapy recommendations for patients at high risk (i.e., Rai stages III-IV) and progressive cytopenia are based on the following:
  - Patient age
  - Patient comorbidities
  - Presence or absence of del(17p)
  - Presence or absence of TP53 mutations

- For first-line treatment of CLL without del(17p) or TP53 mutations, NCCN recommendations (including category 1, which are based on high-level evidence, with uniform NCCN consensus that the intervention is appropriate) are as follows:

  - Patients < 65 years, without significant comorbidities:
    - Preferred regimens: Acalabrutinib ± Obinutuzumab (category 1); Ibrutinib monotherapy (category 1); Venetoclax + Obinutuzumab; Zanubrutinib monotherapy.

    - Other recommended regimens include: FCR (Fludarabine, Cyclophosphamide, Rituximab) (preferred for use in patients with IGHV-mutated CLL); Ibrutinib + Rituximab (category 2B); FR (Fludarabine, Rituximab) (category 3); Bendamustine + Anti-CD20 monoclonal antibody; high-dose Methylprednisone (HDMP) + Rituximab or Obinutuzumab (category 3).

  - Patients ≥65 years, and younger patients with significant comorbidities (creatinine clearance < 70 mL/min):
    - Preferred regimen: Acalabrutinib ± Obinutuzumab (category 1); ibrutinib (category 1); Venetoclax + Obinutuzumab (category 1); Zanubrutinib (category 2A) .

    - Other recommended regimens: Bendamustine (70 mg/m2 in cycle 1 with escalation to 90 mg/m2 if tolerated) + anti-CD20 monoclonal antibody (not recommended for use in frail patients); chlorambucil + Obinutuzumab; Obinutuzumab monotherapy; HDMP + rituximab or Obinutuzumab (category 2B),

Ibrutinib + Obinutuzumab (category 2B), chlorambucil monotherapy (category 3); rituximab monotherapy (category 3).

- Post–first-line maintenance therapy:
  - ℛ Consider Lenalidomide for high-risk patients.

  - ℛ Preferred second line and subsequent therapy regimens for CLL patients without del(17p) or TP53 mutations of all ages and comorbidity status are as follows: Ibrutinib monotherapy (category 1); Venetoclax + rituximab (category 1); acalabrutinib monotherapy (category 1); Zanubrutinib monotherapy.

- Additional second line and subsequent therapy recommended regimens for those >65 years of age or < 65 years of age with multiple comorbidities:
  - ℛ Chlorambucil + rituximab; duvelisib monotherapy; Idelalisib ± Rituximab; Lenalidomide ± Rituximab; Obinutuzumab monotherapy; ofatumumab monotherapy; Venetoclax monotherapy; Bendamustine + Rituximab (category 2B); HDMP+ Rituximab or Obinutuzumab (category 2B); dose-dense Rituximab (category 3).

- Additional second line and subsequent therapy recommended regimens for those < 65 years of age without significant comorbidities:
  - ℛ Bendamustin + Rituximab; Duvelisib monotherapy; FCR; Idelalisib ± Rituximab; Lenalidomide ± Rituximab; Obinutuzumab monotherapy; Ofatumumab monotherapy; Venetoclax monotherapy; HDMP + Rituximab or Obinutuzumab (category 2B); Alemtuzumab ± Rituximab (category 3); Bendamustin, Rituximab + Ibrutinib (category 3); FC (Fludarabine, Cyclophosphamide) + Ofatumumab (category 3).

- For treatment of CLL with del(17p) or TP53 mutations, the NCCN recommends the following:
  - ❖ First-line therapy preferred regimens include:
    - ℛ Acalabrutinib ± Obinutuzumab; Venetoclax + Obinutuzumab; Ibrutinib monotherapy; Zanubrutinib monotherapy.

    - ℛ Other recommended regimens include Alemtuzumab ± Rituximab; HDMP + Rituximab; or Obinutuzumab monotherapy.

- Relapsed/refractory disease therapy:
  - ℛ Ibrutinib (category 1); Venetoclax + Rituximab (category 1); Acalabrutinib (category 1); Venetoclax monotherapy; Zanubrutinib monotherapy

  - ℛ Other recommended regimens include Alemtuzumab ± Rituximab; Lenalidomide ± Rituximab; HDMP + Rituximab; Idelalisib ± Rituximab; Ofatumumab monotherapy; Duvelisib monotherapy.

- Post–first-line maintenance therapy:
  - ℛ Consider lenalidomide for high-risk patients.

- Post–second-line therapy (i.e., for patients with complete or partial response to relapsed/refractory therapy):
  - ℛ Lenalidomide, ofatumumab

- The ESMO guidelines note that patients with del(17p) have a poor response to Fludarabine and short survival and instead recommend initial treatment with Alemtuzumab or Allogeneic stem cell transplantation. ESMO guidelines also recommend Allogeneic stem cell transplantation in patients with very-high-risk TP53 mutation and/or refractory disease.