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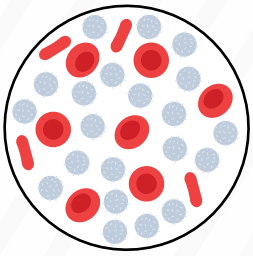
Enhancing Patient Outcomes in Chronic Lymphocytic Leukaemia

Insights on staging, prognostic biomarkers, and emerging treatments



Chronic lymphocytic leukaemia (CLL)—a cancer of B cells—is one of the most common types of leukaemias[1]

CLL is a highly heterogeneous malignancy with significant variability in the disease's course[1]

- Indolent disease not requiring treatment
- Late disease progression occurring several years after diagnosis
- More aggressive variants requiring immediate treatment

Advances in gene sequencing have uncovered novel signalling pathways and molecular biomarkers involved in CLL oncogenesis and progression[1,2]

Clinical, haematological, and molecular biomarkers can aid the risk stratification and prognostication of patients with CLL[1,2]

Diagnosis[3,4]

Complete and differential blood cell count
CLL is defined by the presence of ≥5 × 10^9/L (or 5,000/μL) B lymphocytes in the peripheral blood for >3 months

Medical history

Immunophenotyping to confirm the clonality of circulating B lymphocytes—surface antigen CD5 together with the B cell antigens CD19, CD20, and CD23

Physical examination of lymph node areas and palpable areas of the spleen and liver

Lymph node or bone marrow biopsy may be used to confirm the diagnosis in case of inconclusive microscopy and flow cytometric assessments of peripheral blood

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Staging and prognostication

CLL is staged using the Rai-Binet staging system, which is used to determine prognosis based on haematological features and lymph node involvement[3,4]

- Head and neck
- Axillae
- Groin
- Palpable liver
- Palpable spleen

Binet staging system	
Binet A (low risk)	Haemoglobin (Hb) ≥10 g/dL, platelets ≥100 × 10^9/L, and <3 lymphoid sites
Binet B (intermediate risk)	Hb ≥10 g/dL, platelets ≥100 × 10^9/L, and >3 lymphoid sites
Binet C (high risk)	Hb <10 g/dL and/or platelets <100 × 10^9/L

Binet's system considers five possible sites of involvement: cervical, axillary, and inguinal lymphadenopathy (whether unilateral or bilateral), as well as the spleen and liver

Rai staging system	
Rai 0 (low risk)	Lymphocytosis with leukaemia cells in the blood and/or marrow
Rai I (intermediate risk)	Lymphocytosis and lymphadenopathy
Rai II (intermediate risk)	Lymphocytosis, splenomegaly, and/or hepatomegaly with or without lymphadenopathy
Rai III (high risk)	Lymphocytosis, Hb <11 g/dL, with or without organomegaly/lymphadenopathy
Rai IV (high risk)	Lymphocytosis, platelets <100 × 10^9/L with or without organomegaly/lymphadenopathy

CLL International Prognostic Index (CLL-IPI) combines cytogenetic and molecular biomarkers to determine prognosis[2,5,6]

Patient factors

- Age
- Gender
- Ethnicity

Disease features

- White blood cell count
- Anaemia
- Thrombocytopenia
- Lymph node involvement
- Hepatomegaly
- Splenomegaly
- Increased lymphocyte doubling time

Antigen expression

- CD38
- Zeta chain associated protein 70

Serological markers

- Beta-2 microglobulin
- Lactate dehydrogenase

Genetic markers

- del17p
- *TP53* mutation
- del11q
- del13q
- Trisomy 12
- *NOTCH1* mutation
- DNA methylation
- Complex karyotype
- *SF3B1* mutation
- *BIRC3* mutation
- *BRAF* mutation
- Micro RNAs – miR-223, miR-29c, and miR-155

Immunogenetic markers

- Unmutated immunoglobulin heavy chain variable gene (*IGHV*) status

Low risk | Intermediate risk | Very high risk

CLL-IPI risk groups and clinical implications

CLL-IPI group	Overall survival at 5 years[4]	Clinical consequence[4]
Low risk	93.2%	No need to treat
Intermediate risk	79.3%	No need to treat unless symptomatic
High risk	63.3%	Treat as indicated unless asymptomatic
Very high risk	23.3%	Use targeted chemoimmunotherapy

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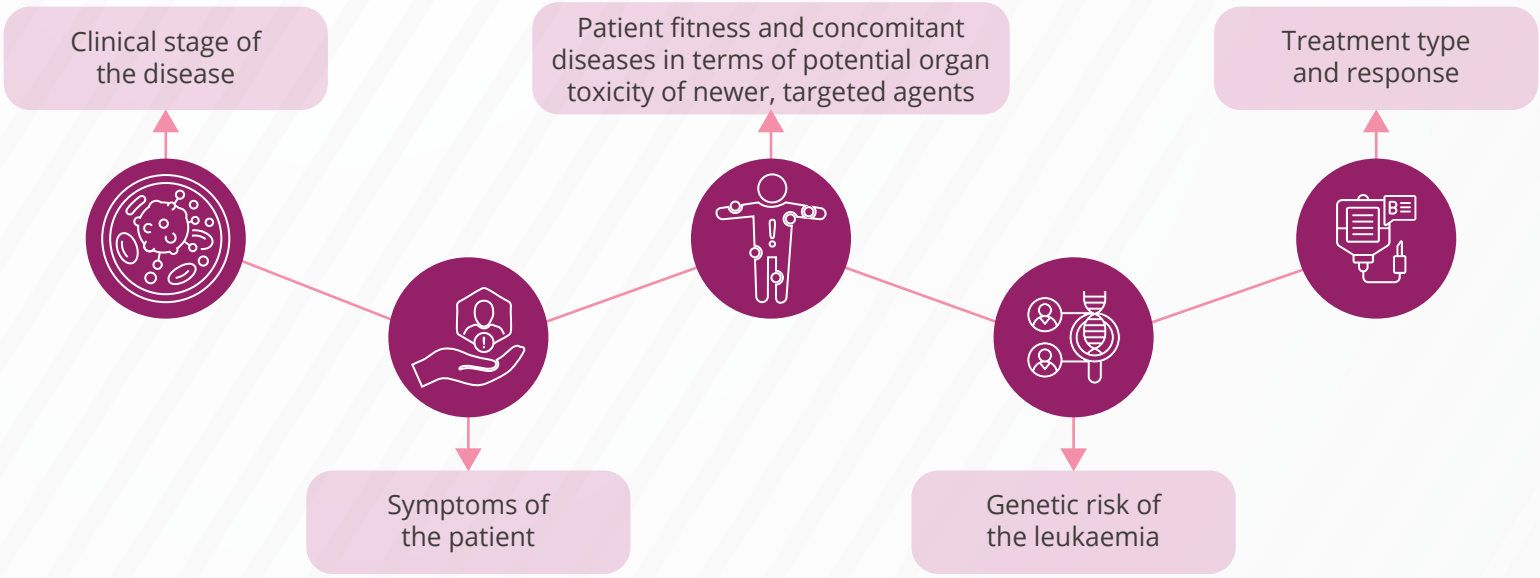
Criteria to define symptomatic disease[3,4]

- Progressive marrow failure — worsening of anaemia and/or thrombocytopenia
- Progressive lymphocytosis
- Weight loss
- Progressive or symptomatic splenomegaly
- Autoimmune complications and poor response to corticosteroids
- Significant fatigue
- Progressive or symptomatic lymphadenopathy
- Symptomatic extranodal involvement
- Fevers and night sweats

Treatment considerations[4]



Treatment of CLL[1,4,6,7]

First-line treatments for CLL

- **Bruton's tyrosine kinase (BTK) inhibitors**
  - Ibrutinib
  - Acalabrutinib
  - Zanubrutinib
- **B-cell lymphoma 2 inhibitor**
  - Venetoclax – used in combination with obinutuzumab for fixed-duration therapy
- **Anti-CD20 monoclonal antibody**
  - Obinutuzumab – often used in combination with venetoclax

Selection depends on patient-specific factors, including genetic mutations (e.g., TP53 status, comorbidities, and overall health)

Later-line treatments for CLL (relapsed/ refractory disease)

- **Alternative BTK inhibitor**
  - Pirtobrutinib
- **BCL-2 inhibitor**
  - Venetoclax – particularly if not used in the first-line setting
- **Phosphoinositide 3-kinase inhibitors**
  - Idelalisib
  - Duvelisib (less commonly used due to safety concerns)
- **Chimeric antigen receptor T-cell therapy**
- **Checkpoint inhibitor**
  - Pembrolizumab (anti-programmed cell death protein 1-1) – under investigation, limited use

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Treatment recommendations[4,6]

Early disease

Patients have good prognosis and do not benefit from treatments

Wait-and-watch strategy remains the standard of care

Advanced disease[6]

Symptomatic early-stage and advanced-stage CLL

IGHV-unmutated, no *TP53* mutation or del(17p)		*IGHV*-mutated, no *TP53* mutation or del(17p)		*TP53* mutation or del(17p)
Fit patients	Unfit patients	Fit patients	Unfit patients	
Ibrutinib chemoimmunotherapy (CIT); fludarabine, cyclophosphamide and rituximab (FCR) [I,A]	Venetoclax + obinutuzumab; ibrutinib oral or acalabrutinib; CIT; chlorambucil plus obinutuzuma (CLBO) [I,A]	CIT; FCR; ibrutinib [I,A]	Venetoclax + obinutuzumab; CIT; CLBO; ibrutinib or acalabrutinib [I,A]	Ibrutinib or acalabrutinib; venetoclax + obiutuzumba venetoclax; idelalisib + rituximab [III, A]

Symptomatic relapsed CLL

TP53 mutation or del(17p)	Short remission duration (<36 months)	Long emission duration (>3 months)
• Ibrutinib or acalabrutinib [I, A] • Venetoclax + rituximab [I, A] • Venetoclax alone [III, B] • Idelalisib + rituximab [III, B] • Consider allogeneic stem cell transplantation in fit patients	• Ibrutinib or acalabrutinib [I, A] • Venetoclax + rituximab [I, A] • Venetoclax alone [III, B] • Idelalisib + rituximab [III, B]	• Repeat front-line [II,B] or change to ibrutinib or acalbrutinib • Venetoclax + rituximab • Idelalisib + rituximab CIT

Treatment challenges[4,6]

- Selection of the optimal treatment regimen
- Resistance to therapy
- Refractory disease
- Biomarkers with conflicting prognostic significance
- Minimal residual disease and relapse

Key messages

- **Advanced prognostication and risk stratification models that combine emerging cytogenetic and molecular markers with clinical features of CLL can aid the selection of optimal treatment regimens**
- **Combining established and investigation therapies using a personalised treatment approach may help improve patients' survival and quality of life**

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