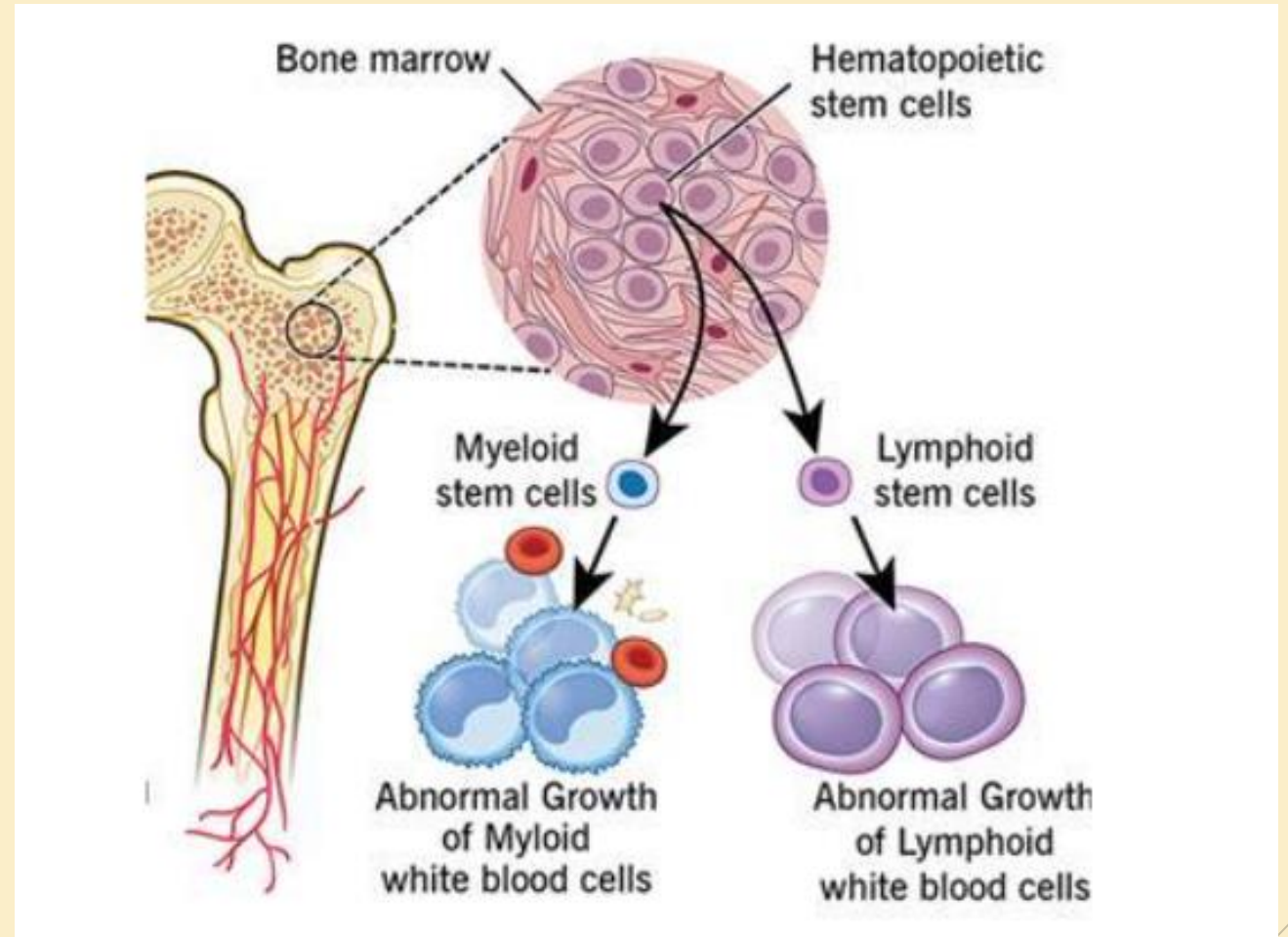


CHRONIC LEUKEMIA

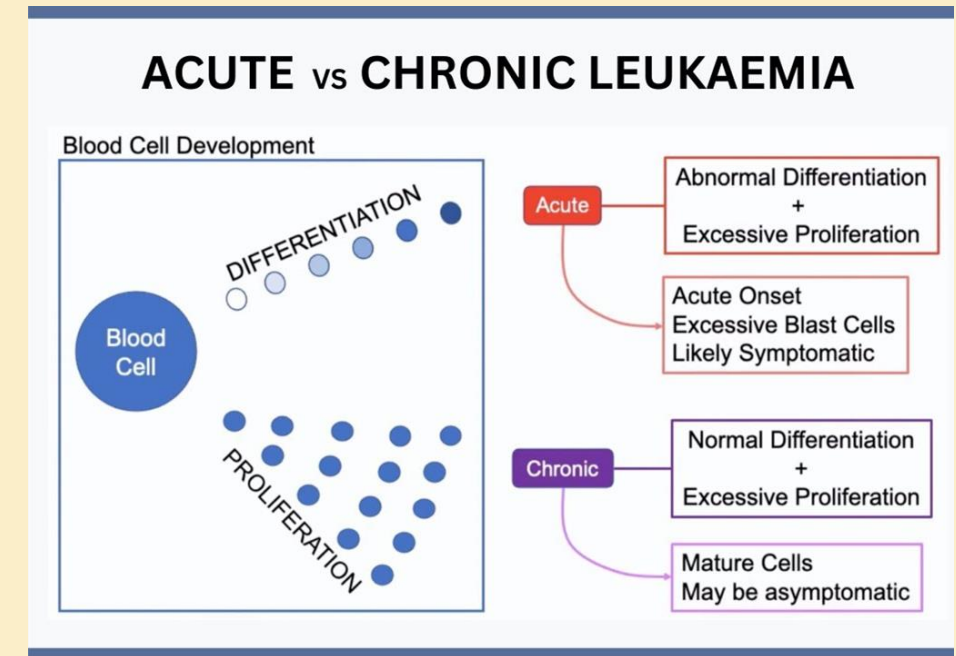
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- Chronic leukemias are slowly progressing cancers of the blood and bone marrow that involve mature or maturing hematopoietic cells.
 - OR
- Chronic leukemias are clonal hematologic malignancies characterized by the slow proliferation of mature or maturing cells from either the myeloid or lymphoid lineage.
- Chronic leukemias are
 - Slow onset, indolent course
 - Cells involved are more differentiated
 - Often detected incidentally during routine blood work

Common chronic leukemias include:

1. Chronic Myeloid Leukemia (CML)
2. Chronic Lymphocytic Leukemia (CLL)
3. Hairy Cell Leukemia
4. Prolymphocytic Leukemia



Chronic Myeloid Leukemia (CML)

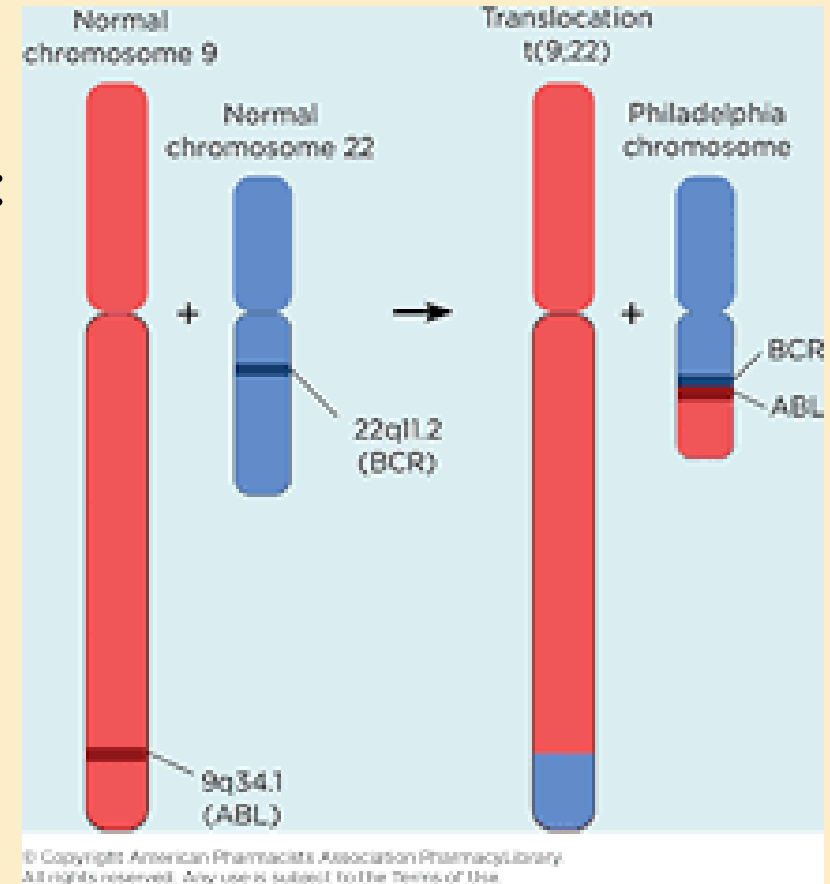
- CML is a clonal myeloproliferative disorder characterized by the uncontrolled proliferation of mature and maturing granulocytic cells (neutrophils, basophils, eosinophils) in the bone marrow and peripheral blood.
- It arises from the malignant transformation of a pluripotent hematopoietic stem cell.
- The disease is cytogenetically defined by the Philadelphia chromosome (Ph), which produces the BCR-ABL fusion oncogene.

Epidemiology

- Accounts for 15–20% of adult leukemias
- More common in men than women
- Median age at diagnosis: 67 years
- Rare in children; more common in adults

Etiology

- CML is mainly caused by a specific genetic mutation rather than environmental or inherited factors.
- **Philadelphia chromosome (Ph)** formation causes CML
This chromosome is produced by a **translocation** between:
Chromosome 9 (ABL gene)
Chromosome 22 (BCR gene)
- **No association with:**
 1. Heredity or family history
 2. Geography
 3. Ethnicity or race
 4. Socioeconomic status
- **Associated Risk Factor:**
 - Exposure to ionizing radiation
 - Seen in atomic bomb survivors (Hiroshima and Nagasaki)
 - Higher incidence in patients exposed to therapeutic radiation



Pathophysiology

1. Philadelphia Chromosome (Ph) and BCR-ABL formation

- Ph results from a reciprocal translocation between:
 - Chromosome 9 (region q34) carrying the ABL gene
 - Chromosome 22 (region q11) carrying the BCR gene
 - Symbolized as t(9;22)(q34;q11)
- This creates the BCR-ABL fusion gene on the shortened chromosome 22 (Philadelphia chromosome)

2. Formation of BCR-ABL Protein

- The BCR-ABL gene codes for a fusion protein with constitutive tyrosine kinase activity
 - Promotes uncontrolled cell division
 - Inhibits apoptosis (via Fas pathway)
 - Alters cell adhesion and DNA repair

Mechanism:

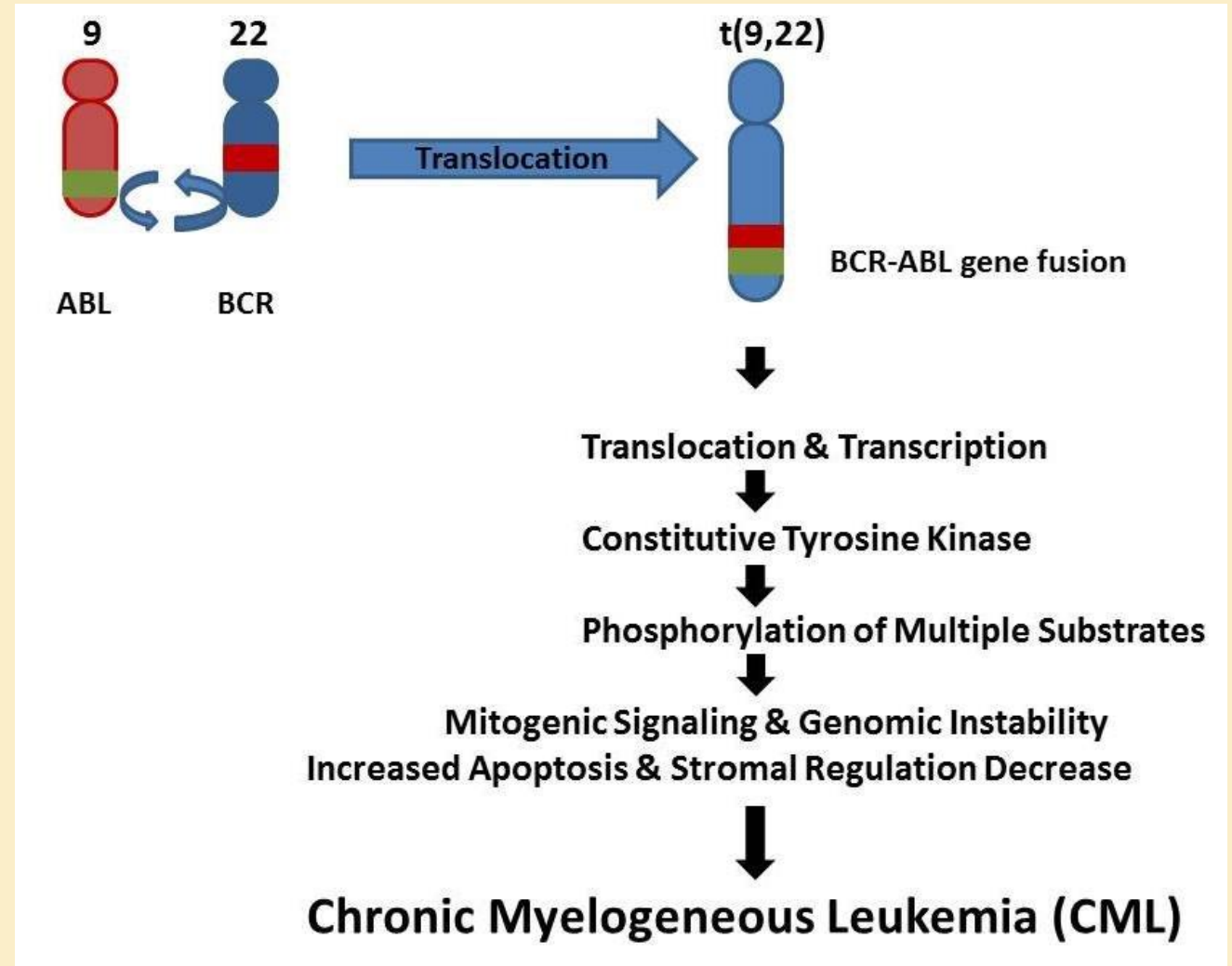
Normal ABL Function	BCR-ABL Abnormality
Controlled cell growth	Uncontrolled proliferation
Regulated by cell signals	Escape from normal control mechanisms
Promotes apoptosis	Inhibits apoptosis (anti-Fas signaling)

3. Clonal Hematopoiesis

- CML arises from one pluripotent hematopoietic stem cell
- This transformed clone expands abnormally, displacing normal hematopoiesis
- Hyperproliferation of granulocytes and their precursors
- Affected lineages include:
 - Myeloid (granulocytes, monocytes, erythrocytes, megakaryocytes)
 - Sometimes lymphoid (T and B cells)
 - Thus, Ph⁺ cells are found in multiple hematopoietic lineages

4. Disease Phases of CML

Phase	Features
Chronic Phase (CP)	Increased mature granulocytes; often asymptomatic
Accelerated Phase (AP)	Increased blasts, cytogenetic abnormalities, worsening symptoms
Blast Crisis (BC)	$\geq 20\%$ blasts in blood or marrow; resembles acute leukemia



5. Molecular Targeting of BCR-ABL Tyrosine Kinase

- The BCR-ABL protein is a tyrosine kinase, and targeting this enzyme was a major breakthrough.
- BCR-ABL creates a constitutively active tyrosine kinase, critical for disease pathogenesis

Mechanism of TKI (e.g., Imatinib)

- Binds to the ATP-binding site of the tyrosine kinase domain
- Prevents phosphorylation of downstream targets
- Stops cell signaling required for proliferation
- ATP binds to BCR-ABL's kinase domain and activates signaling for:
 - Proliferation, Survival, Anti-apoptosis

6. Second-Generation TKIs

- Used when resistance or intolerance to imatinib occurs or as frontline therapy:
 1. Dasatinib
 2. Nilotinib
 3. Bosutinib
- Third-generation TKI:
 - Ponatinib (active against T315I mutation)

Clinical Presentation of CML

- Chronic Myeloid Leukemia (CML) progresses through three distinct clinical phases: Chronic Phase (CP), Accelerated Phase (AP), and Blast Crisis (BC).
- Most patients are diagnosed in the Chronic Phase, which typically has an indolent course and favorable prognosis with treatment.

Common Signs and Symptoms

Symptom	Mechanism
Fatigue, weight loss, night sweats	Cytokine-mediated effects of leukemia
Left upper quadrant pain, early satiety	Splenomegaly
Bone pain	Marrow expansion
Abdominal pain, priapism, visual changes, confusion	Leukostasis from extreme leukocytosis
Gout, uric acid stones	Hyperuricemia from high cell turnover

DIAGNOSIS of CML

2. Laboratory test

1. Physical Examination Findings

- Splenomegaly (common)
- Hepatomegaly
- Occasionally lymphadenopathy

Test	Typical Findings
Complete Blood Count (CBC)	Leukocytosis (WBC often $>100,000/\text{mm}^3$), thrombocytosis, basophilia
Peripheral Blood Smear	Left shift with all stages of granulocyte maturation
Serum Biochemistry	↑ Uric acid, ↑ LDH
Leukocyte Alkaline Phosphatase (LAP) Score	Typically low or absent

3. Bone Marrow Biopsy

Parameter	Finding
Cellularity	Markedly hypercellular (75–90%)
Myeloid: Erythroid Ratio	Increased (10–30:1)
Blasts	<10% in CP
Megakaryocytes	Increased but normal morphology
Fibrosis	Typically absent or minimal

4. Cytogenetics and Molecular Diagnostics

Test	Purpose
Karyotyping	Detect Philadelphia chromosome (t[9;22][q34;q11])
FISH (Fluorescence In Situ Hybridization)	Detect BCR-ABL fusion gene
RT-PCR (Quantitative PCR)	Measure BCR-ABL1 transcript levels using International Scale (IS) for monitoring response to treatment

Clinical Presentation and Diagnosis of Chronic Myeloid CML

Clinical Presentation



General Facts

- 90% patients a diagnosed in CP
- 50% are asymptomatic at diagnosis
- Often discovered incidentally on routine blood work

Common Signs and Symptoms:

Symptom	Machanism
Fatigue weight, loss	Cytokine-mediated effects of leukemia
Left upper quadrant pain	Splenomegaly
Bone pain	Marrow expansion
Abdominal pain, priapism, visual changes	Leukostasis from extreme leukocytosis i-Ap cell turnover
Gout, uric acid stones hyperkalemia	Hyperuricemia (high cell turnover)

Physical Examination Findings

- Splenomegaly (common)
- Hepatomegaly
- Occasionally lymphadenopathy



Diagnosis of CML

Test	Typical Findings
Complete Blood Count (CBC)	Leukocytosis (WB, often $>10.00/\text{mm}^3$), thrombocytosis
Peripheral Blood Smear	Left shift with stages of granulocyte maturation
Serum Biochemistry	Elevated uric acid and lactate dehydrogenase
Leukocyte Alkaline Phosphatase (Dvl-score)	Typically absent or minimal
Cytogenetics and Molecular Diagnostics	
Purpose	
Karyotyping	Detect Philadelphia chromosome
FISH (Fluorescence in Situ Hybridization)	Detect BCR ABL fusion gene
RT-PCR (Quantitative PCR)	Measures BCR _{ABL} transcript levels using International Scale (IS) for re-monitoring response to treat

Phases of CML and Key Diagnostic Criteria

Phase	Blast Count	Other Findings
Chronic Phase	$< 10\%$ blasts	Typically asymptomatic, responsive to TKIs
Accelerated Phase (AP)	$10\text{--}19\%$ blasts	Progressive disease, therapy resistance Increased basophils, extramedullary evolution
Blast Crisis (BC)	$> 20\%$ blasts	Acute leukemia-like, Extramedullary disease, rapid fatal progression

TREATMENT AND MANAGEMENT OF CML

1. Treatment Goals in CML

1. Eradicate the leukemic clone from the bone marrow.
2. Maintain chronic phase (CP) as long as possible.
3. Minimize treatment-related toxicity.
4. Achieve and maintain deep molecular response.
5. Prevent or delay progression to accelerated phase (AP) or blast crisis (BC).

2. Tyrosine Kinase Inhibitors (TKIs) – Mainstay of Therapy

First-Generation TKI: Imatinib

- Standard initial dose: 400 mg orally once daily.
- Binds ATP-binding site of BCR-ABL tyrosine kinase.
- Proven to induce high rates of complete hematologic, cytogenetic, and molecular responses.
- IRIS trial: 10-year survival ~83%.

Response Monitoring Timelines:

3 months: Complete hematologic response.

6 months: Partial cytogenetic response.

12 months: Complete cytogenetic response.

18 months: Major molecular response (MMR).

Imatinib Toxicities:

- Myelosuppression (most common).
- GI upset, edema, rash, hepatotoxicity.
- Interacts with CYP3A4 metabolized drugs.

3. Advanced-Generation TKIs

◆ **Dasatinib**

- Dose: 100 mg once daily (CP), 140 mg daily (AP/BC).
- Active against many imatinib-resistant mutations except T315I.
- Can cause pleural effusions, cytopenias, rash.

◆ **Nilotinib**

- Dose: 300-400 mg twice daily.
- More potent than imatinib.
- Risk of QTc prolongation, hyperbilirubinemia.

◆ **Bosutinib**

- Dose: 500 mg daily.
- Fewer off-target effects.
- Common side effects: diarrhea, rash.

◆ **Ponatinib**

- Dose: 45 mg daily, effective against T315I mutation.
- Black box warning: vascular occlusion, liver failure.
- Reserved for T315I-positive or TKI-refractory CML.

4. Response Assessment

Types of Responses:

- Hematologic: Normal blood counts.
- Cytogenetic: % of Ph⁺ cells in marrow.
- Molecular: BCR-ABL mRNA by RT-PCR (on International Scale).

Molecular Response Milestones:

- Early molecular response (EMR): BCR-ABL <10% at 3–6 months.
- Major molecular response (MMR): BCR-ABL <0.1% (3-log reduction).
- Complete molecular response (CMR): Undetectable BCR-ABL.

Monitoring:

- RT-PCR for BCR-ABL every 3 months.
- Bone marrow cytogenetics if molecular targets not met.

5. Resistance to TKIs

- **Mechanisms:**
 - BCR-ABL point mutations (e.g., T315I).
 - Gene amplification.
 - P-glycoprotein overexpression, clonal evolution.
- **Mutation analysis** is done if:
 - Loss of response.
 - Failure to meet milestones.
 - Progression to AP/BC.

6. Conventional Cytotoxic Chemotherapy (For Leukoreduction)

- Hydroxyurea: Rapidly lowers WBC count in newly diagnosed CP-CML.
- Dose: 40–50 mg/kg/day until WBCs $<10,000/\text{mm}^3$.
- Discontinue once TKIs are started.
- Busulfan is obsolete due to pulmonary toxicity.

7. Interferon-Alpha (IFN- α)

- Previously standard before TKIs.
- Now limited to:
 - Patients intolerant or resistant to TKIs.
 - Post-HSCT relapse.
- Combined with TKIs in clinical trials.
- Significant toxicity: flu-like symptoms, depression, autoimmune issues.

8. Omacetaxine Mepesuccinate

- Approved for CML resistant to ≥ 2 TKIs or with T315I mutation.
- SC injection: 1.25 mg/m² BID $\times$ 14 days induction.
- MOA: Inhibits protein synthesis $\rightarrow$ reduces BCR-ABL and Mcl-1.
- Used in CP or AP CML.

9. Hematopoietic Stem Cell Transplantation (HSCT)

- Allogeneic HSCT: Only curative option.
- Best outcomes in younger patients with early CP.
- 5-year survival:
 - Matched sibling donor: ~70–80%.
 - Matched unrelated donor: ~40–70%.
- Limitations:
 - Only ~30% of patients have sibling donors.
 - Transplant-related mortality increases with age (>50 years).
 - GVL effect plays a key role in long-term remission.

Chronic Lymphocytic Leukemia (CLL)

- Chronic Lymphocytic Leukemia (CLL) is a lymphoproliferative disorder characterized by a progressive accumulation of functionally incompetent, clonal B lymphocytes in the blood, bone marrow, and lymphoid tissues.
- These abnormal B cells typically co-express CD5, CD19, and CD23 and have low levels of surface immunoglobulins (IgM and IgD).

Epidemiology

1. Most common leukemia in Western countries, particularly the United States.
2. Incidence (US): Approximately 20,720 new cases in 2019.
3. Age:
 - a. Median age at diagnosis: 71 years.
 - b. Around 20–30% of cases occur in patients younger than 55 years.
4. Sex: Male predominance (about 2:1 male-to-female ratio).
5. Ethnicity: Higher incidence among White populations.
6. Familial risk:
 - a. First-degree relatives of CLL patients have a 3-fold increased risk of developing CLL or other lymphoid malignancies.

Etiology (Risk Factors)

The exact cause of CLL is unknown, but several risk factors have been identified:

1. Genetic predisposition: Family history of CLL or lymphoid malignancies.
2. Male sex
3. Advanced age
4. White race
5. Environmental and occupational exposures
6. Monoclonal B-cell lymphocytosis (MBL):
 - a. Considered a precursor condition.
 - b. Patients with MBL have clonal B cells in their blood with CLL-like immunophenotype.
 - c. MBL precedes the development of CLL in almost all cases and can be detected 6 months to 6.4 years before diagnosis.

Pathophysiology

CLL is characterized by:

1. Clonal expansion of B cells

- a. Derived from CD5+ B lymphocytes (unusual because CD5 is typically a T-cell marker).
- b. These cells express low levels of surface IgM and IgD, and co-express CD5, CD19, and CD23.
- c. Functionally incompetent – poor antibody production and impaired immune function.

2. Defective apoptosis

- a. CLL cells accumulate due to impaired programmed cell death rather than high proliferation.
- b. Overexpression of anti-apoptotic genes, such as:
 - i. BCL-2
 - ii. BCL-1
- c. Loss of tumor suppressor genes, such as:
 - i. RB1

3. Role of B-cell receptor (BCR) signaling

- BCR signaling is a key driver of CLL cell survival.
- Bruton's tyrosine kinase (BTK) plays a crucial role:
 - Activates downstream pathways
 - Promotes survival, proliferation, chemokine signaling, and cell migration.

4. PI3K Pathway

- Phosphatidylinositol 3-kinase (PI3K), especially the delta (δ) isoform, is hyperactive.
- Regulates:
 - Cell motility
 - Survival
 - Proliferation

5. Genetic abnormalities

- Cytogenetic changes are observed in about 80% of patients:
 - Common abnormalities: Deletions on chromosomes 11q, 12, 13q, and 17p
 - 17p deletion (TP53) is associated with poor prognosis and treatment resistance.
- Somatic mutations in genes involved in:
 - Cell cycle/DNA repair
 - Intracellular signaling
 - RNA splicing
- These mutations can guide prognosis and therapy selection

6. Transformation to aggressive lymphoma (Richter's Syndrome)

- Occurs in 4–10% of CLL patients.
- Transformation to diffuse large B-cell lymphoma (DLBCL).
- Triggered by:
 - Additional cytogenetic mutations
 - Epstein-Barr virus (EBV) infection

Staging

Rai Staging System (used in the U.S.)

Rai Stage	Clinical Features	Risk	Median Survival
0	Lymphocytosis only	Low	>10 years
I	Lymphocytosis + lymphadenopathy	Intermediate	~7 years
II	+ Organomegaly (hepatomegaly and/or splenomegaly)	Intermediate	~7 years
III	+ Anemia (Hb <11 g/dL)	High	2–4 years
IV	+ Thrombocytopenia (platelets <100,000/ μ L)	High	2–4 years

Clinical Presentation of CLL

A. Constitutional (Systemic) Symptoms

1. These are nonspecific and may indicate disease progression:
2. Fever (unexplained)
3. Fatigue (most common symptom affecting quality of life)
4. Unintentional weight loss
5. Night sweats
6. These symptoms often reflect disease burden or cytokine release.

B. Physical Examination Findings

1.Lymphadenopathy

Commonly involves cervical, axillary, and inguinal nodes.

2.Splenomegaly

- a. May cause early satiety or abdominal discomfort.

3.Hepatomegaly

C. Laboratory Findings

1. Peripheral Blood

- a. Absolute lymphocytosis: Lymphocyte count often $>5,000/\mu\text{L}$
- b. Anemia: can be due to: Autoimmune hemolytic anemia (Coombs +)
- c. Thrombocytopenia: due to marrow suppression
- d. Hypo- or hypergammaglobulinemia:
- e. Monoclonal gammopathy (rare, $<5\%$ of cases)

1. Bone Marrow

- a. Hypercellular marrow
- b. Increased mature lymphocytes
- c. Increased megakaryocytes
 - i. May indicate compensatory response to thrombocytopenia

TREATMENT AND MANAGEMENT OF CLL

Treatment Goals in CLL

1. Achieve and maintain prolonged remission.
2. Minimize treatment-related toxicity.
3. Delay disease progression.
4. Preserve the patient's quality of life
5. Cure is not the primary goal in most patients.

Indications for initiating therapy :

1. Symptomatic disease: B symptoms (fever, night sweats, fatigue, weight loss).
2. Threatened organ function (e.g., organomegaly causing dysfunction).
3. Bone marrow failure: anemia (Hb < 11 g/dL), thrombocytopenia (platelets < 100,000/mm³).
4. Bulky disease (massive splenomegaly or lymphadenopathy).
5. Rapid lymphocyte doubling time (< 6 months).
6. High-risk cytogenetics (e.g., del(17p), TP53 mutations).
7. Asymptomatic early-stage CLL (Rai 0 or Binet A) is **observed**, not treated ("watch and wait").

Therapeutic Approaches

1. Cytotoxic Chemotherapy

a. Alkylating Agents

1. Chlorambucil

- a. Historical agent; still used in frail or elderly patients.
- b. No OS benefit over observation in early-stage disease.
- c. Often used in elderly or frail patients.
- d. Dose:** 15–40 mg/m² orally every 28 days or 4–8 mg/m²/day.

2. Cyclophosphamide

- a. Given orally (1–3 mg/kg/day).
- b. Risk: hemorrhagic cystitis, bladder cancer with prolonged use.

B. Purine Analogs

- **Fludarabine**

- Highly active against CLL.
- **Dose:** 25–30 mg/m² IV daily for 5 days.
- Greater CR rates than chlorambucil but more **immunosuppression**.
- Risk of **neutropenia, viral reactivations** (HSV, VZV).

- **Others:** Cladribine and Pentostatin (less commonly used)

C. Bendamustine

- Has properties of both alkylating agents and purine analogs.
- Higher response rates than chlorambucil (CR: 31% vs 2%).
- Toxicities: **myelosuppression, GI, rash**.

2. Monoclonal Antibody-Based Biologic Therapy

1. Anti-CD20 Antibodies

- **Rituximab:** Chimeric anti-CD20
 - Limited efficacy as monotherapy due to low CD20 expression in CLL.
- **Ofatumumab:** Fully human anti-CD20
 - Active in fludarabine- and alemtuzumab-refractory disease.
- **Obinutuzumab:** Glycoengineered, type II anti-CD20
 - Stronger direct cell killing.
 - Superior PFS when combined with chlorambucil or venetoclax vs rituximab.

1. Anti-CD52 Antibody

a. Alemtuzumab

- i. Active in del(17p) or fludarabine-refractory CLL.
- ii. High risk of pancytopenia, opportunistic infections (requires prophylaxis).

3. Targeted Therapy

a. BTK Inhibitors

- **Ibrutinib**
 - Irreversibly inhibits Bruton's tyrosine kinase (BTK).
 - Highly effective even in del(17p)/TP53-mutated disease.
 - Toxicities: Atrial fibrillation, bleeding, tumor lysis syndrome, lymphocytosis (benign).
 - Resistance: BTK C481S or PLC γ 2 mutations.
- **Acalabrutinib**
 - More selective BTK inhibitor (fewer off-target effects).
 - Better tolerated (fewer cardiac side effects).
 - Not effective in BTK-resistant cases.

b. PI3K Inhibitors

- **Idelalisib (PI3K δ)**
- **Duvelisib (PI3K δ/γ)**
 - Used with rituximab in relapsed/refractory CLL.
 - Serious toxicities: hepatotoxicity, colitis, pneumonitis, infection.
 - Requires infection prophylaxis (PJP, CMV monitoring).

c. BCL-2 Inhibitor

- **Venetoclax**
 - Induces apoptosis by inhibiting BCL-2.
 - Effective in del(17p) and refractory CLL.
 - Tumor lysis syndrome (TLS) risk: requires slow dose ramp-up.
 - Combination with rituximab or obinutuzumab is highly effective.

Role of Hematopoietic Stem Cell Transplantation (HSCT)

- Allogeneic HSCT: Potentially curative but limited to younger patients with high-risk, refractory disease.
- Risks: GVHD, high treatment-related mortality.
- Not commonly used now due to availability of effective targeted therapies.
- Indications:
 - Young, fit patients with TP53 mutations or refractory disease
 - Consider non-myeloablative transplant in elderly

Combination Regimens

Regimen	Components	Use	Key Notes
FCR	Fludarabine + Cyclophosphamide + Rituximab	Fit, younger patients	High CR rate; risk of infections, cytopenias
BR	Bendamustine + Rituximab	Alternative to FCR in elderly	Better tolerated, slightly lower PFS
Ibrutinib + Obinutuzumab	For elderly or unfit	Longer PFS vs Obinutuzumab + Chlorambucil	
Venetoclax + Rituximab (VR)	Relapsed/refractory CLL	Superior to BR (longer PFS, OS benefit)	
Venetoclax + Obinutuzumab (VO)	First-line therapy	Approved for treatment- naïve CLL	