JSC "MEDICAL UNIVERSITY ASTANA
DEPARTMENT OF INTERNAL DISEASES №1

SIW

SUBJECT: CHRONIC LYMPHOCYTIC LEUKEMIA

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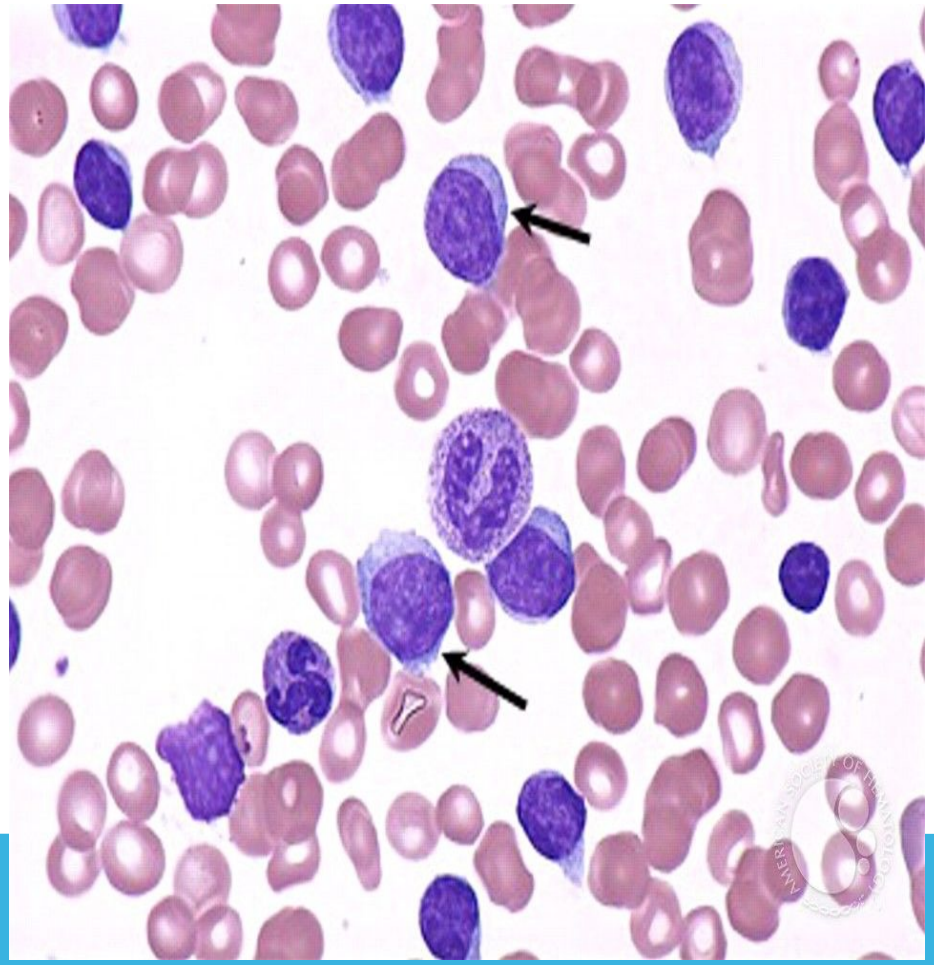
CHRONIC LYMPHATIC LEUKEMIA

Definition:

CLL is a neoplastic disease characterized by proliferation and accumulation (blood, marrow and lymphoid organs) of morphologically mature but immunologically dysfunctional lymphocytes



CLL - EPIDEMIOLOGY

- Most common leukemia of Western world.
- Less frequent in Asia and Latin America.
- Male to female ratio is 2:1.
- Median age at diagnosis is 65-70 years.
- Uncommon (10%) in patients under 50 years
- In US population incidence is similar in different races.

CLL – ETIOLOGY

The cause of CLL is unknown

There is increased incidence in farmers, rubber manufacturing workers, asbestos workers, and tire repair workers

Genetic factors have been postulated to play a role in high incidence of CLL in some families

Cytogenetics

- clonal chromosomal abnormalities are detected in approximately 50% of CLL patients
- the most common clonal abnormalities are:
  - trisomy 12

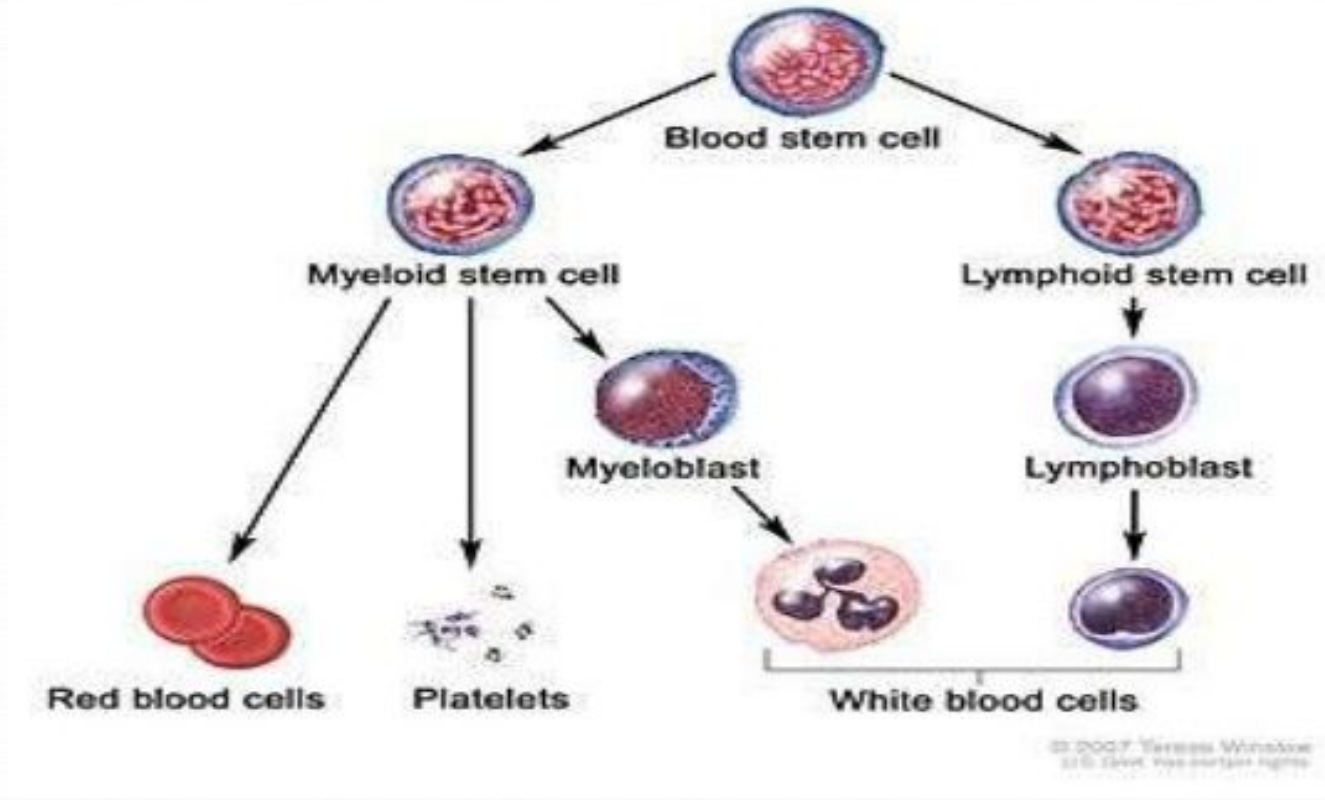
structural abnormalities of chromosomes 13, 14 and 11

patients with abnormal karyotypes have a worse prognosis

Oncogenes

- in most cases of CLL is overexpressed the proto-oncogene c-fgr 9a member of the src gene family of tyrosine kinases

PATHOPHYSIOLOGY



CLL – INITIAL SYMPTOMS

Approximately 40% are asymptomatic at diagnosis – discovered by a CBC

In symptomatic cases the most common complaint is fatigue

Well's syndrome – increase sensitivity to insects bites

B symptoms – fever, sweats, weight loss

Less often the initial complaint are enlarged nodes or the development of an infection (bacterial)

CLL - Clinical findings

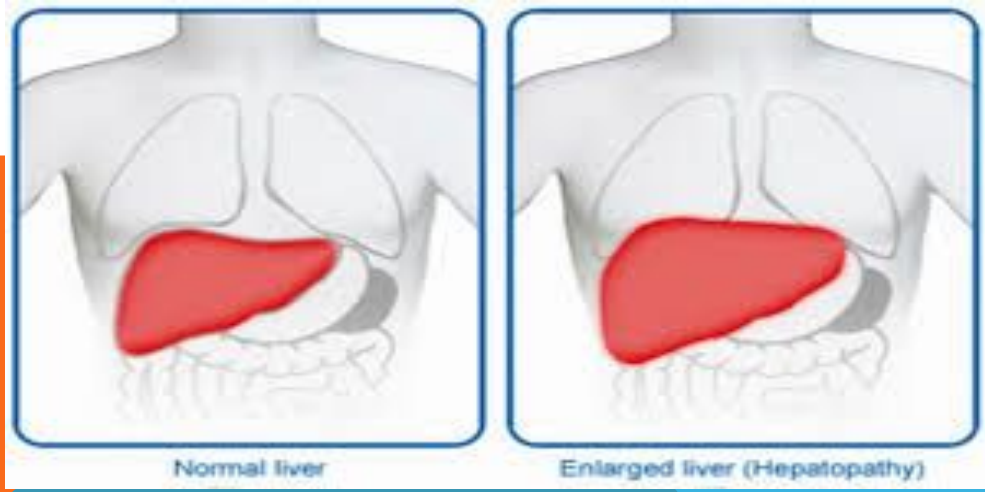
Most symptomatic patients have enlarged lymph nodes (more commonly cervical and supraclavicular) and splenomegaly

The lymph nodes are usually discrete, freely movable, and nontender

Hepatomegaly may occure

Less common manifestation are infiltration of tonsils, mesenteric or retroperitoneal lymphadenopathy, and skin infiltration

Patients rarely present with features of anemia, and bruising or bleeding



CLL – LAB FINDINGS

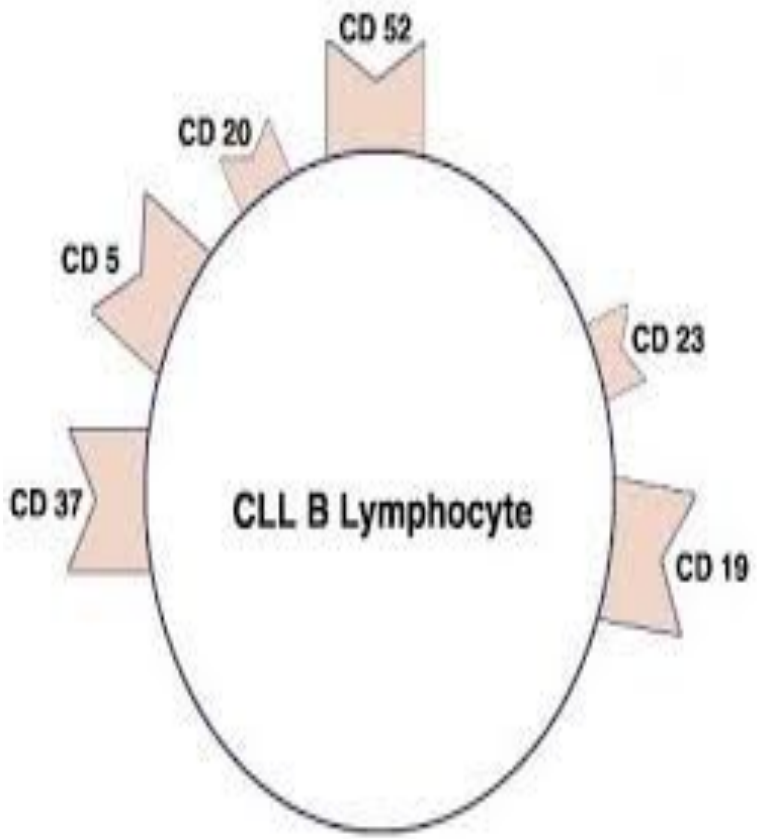
a) Blood test lymphocytosis ≥ 5G/l (4 weeks)

b) Morphology monoconal population of small mature lymphocyte

c) B-cell CLL phenotype clonal CD5+/CD19+ population

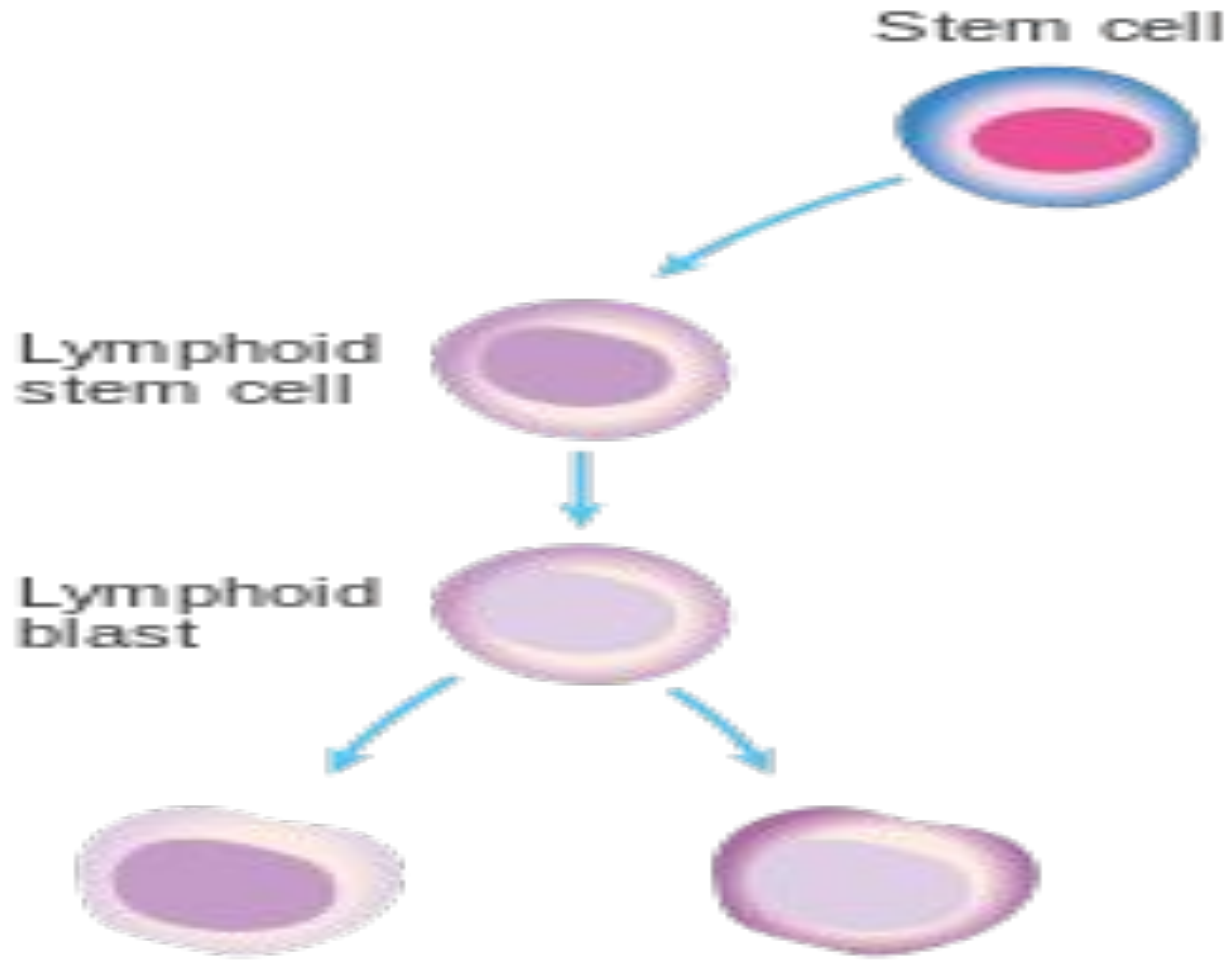
of lymphocyte

d) Markers of clonality κ/λ light chain restriction; cytogenetical abnormalities



e) Bone marrow infiltrate > 30% of nuceated cells on aspirate

f) Lymph node diffuse infiltrate of small lymphocye


Stem cell
Lymphoid stem cell
Lymphoid blast
B lymphocyte
T lymphocyte
CLL affects these B cells

CLL - LABORATORY FINDINGS (2)

Clonal expansion of B (99%) or T(1%) lymphocyte

In B-cell CLL clonality is confirmed by

the expression of either □ or □ light chains on the cell surface membrane

the presence of unique idiotypic specificities on the immunoglobulins produced by CLL cells

by immunoglobulin gene rearrangements

typical B-cell CLL are unique in being CD19+ and CD5+

CLL - IMMUNOPHENOTYPE

Detect antigens on surface of cells

Specific antibodies

Use flow cytometry or immunohistochemistry

CLL = mature B cells

CD5

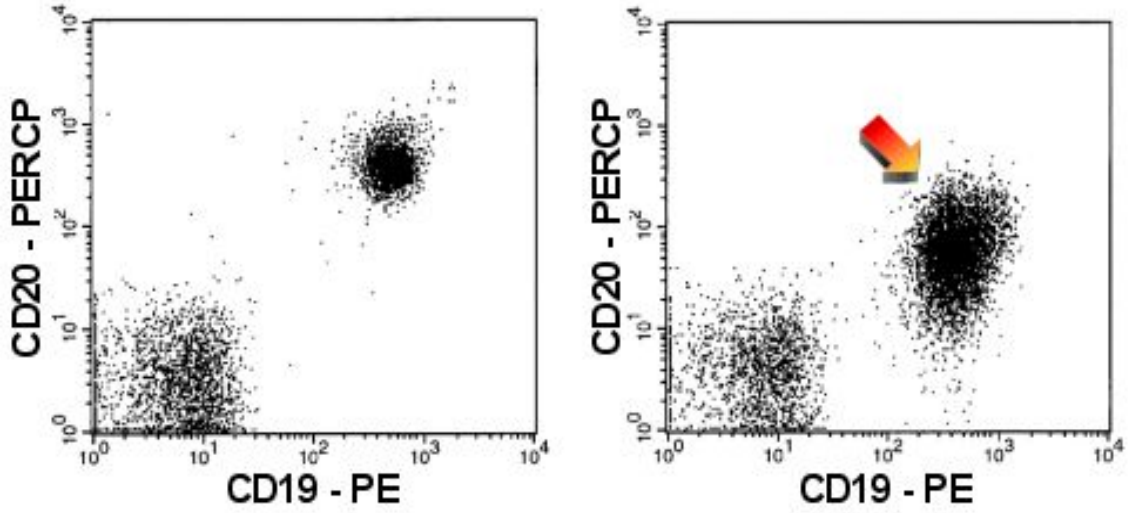
CD19

CD20 - low

CD22 - low

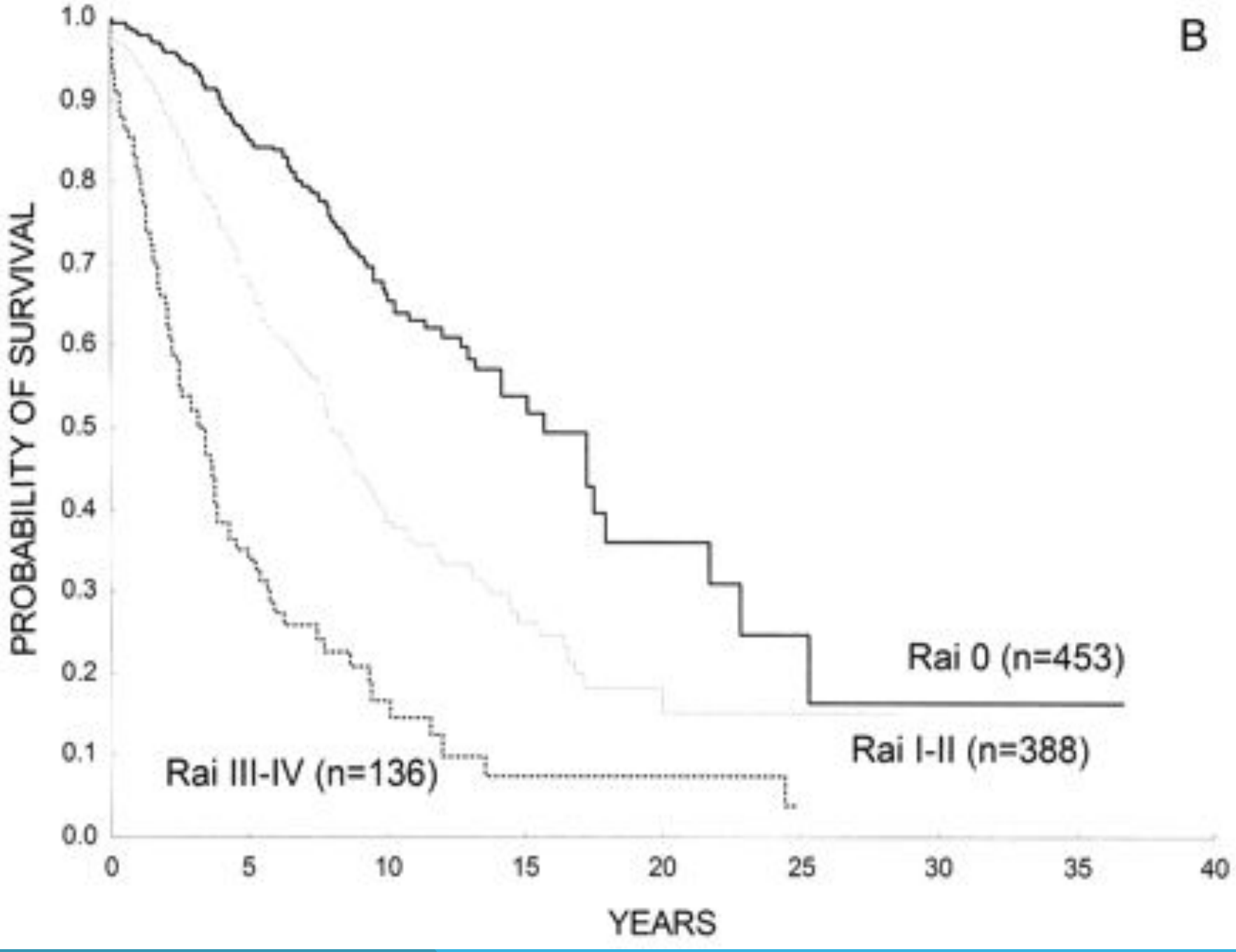
CD23

Light chains (κ, λ)



CLL – RAI STAGING SYSTEM

Stage	Features	Risk
0	•Lymphocytosis	Low
I	•Lymphocytosis •Enlarged LN	Intermediate
II	•Lymphocytosis •Hepatomegaly or splenomegaly •±enlarged LN	Intermediate
III	•Lymphocytosis •Anemia •±hepatomegaly, splenomegaly, or enlarged LN	High
IV	•Lymphocytosis •Thrombocytopenia •±hepatomegaly, splenomegaly, enlarged LN, or anemia	High


B
PROBABILITY OF SURVIVAL
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5
10
15
20
25
30
35
40
YEARS
Rai 0 (n=453)
Rai I-II (n=388)
Rai III-IV (n=136)

CLL – BINET STAGING SYSTEM

Stage	Features	Corresponding Rai Stages
A	<3 areas of enlarged lymphoid tissue	0, I, II
B	>3 areas of enlarged lymphoid tissue	I, II
C	anemia + thrombocytopenia	III, IV

Clinical staging systems for CLL

Value	Stage: Rai	Stage: Binet	Median survival
Lymphocytosis (>15,000/mm^3)	0	-	150 months (12.5 years)
Lymphocytosis plus nodal involvement	I	A <3 node groups	101-108 months (8.5-9 years)
Lymphocytosis plus organomegaly	II	B >3 node groups	60-71 months (5-6 years)
Anemia (RBCs)	III Hgb <11 g/dL	C Hgb <10 g/dL	19-24 months (1.5-2 years)
Lymphocytosis plus thrombocytopenia (platelets)	IV PLT <100,000/mm^3	PLT <100,000/mm^3	

CLL – TREATMENT (1)

- Watch and wait
- Monotherapy
- glucocorticoids
- alkylating agents (Chlorambucil, Cyclophosphamide)
- purine analogues (Fludarabine, Cladribine, Pentostatin)
- Combination chemotherapy
- Chlorambucil/ Cyclophosphamide + Prednisone
- Fludarabine + Cyclophosphamide +/- Mitoxantrone
- CVP, CHOP
- Monoclonal antibodies (monotherapy and in combination)
- Alemtuzumab (anti-CD52)
- Rituximab (anti-CD20)
- Splenectomy
- Radiotherapy

CLL – TREATMENT (2)

Hematopoietic stem cell transplantation

- allogeneic with reduced intesity conditioning
- autologous

New and novel agents

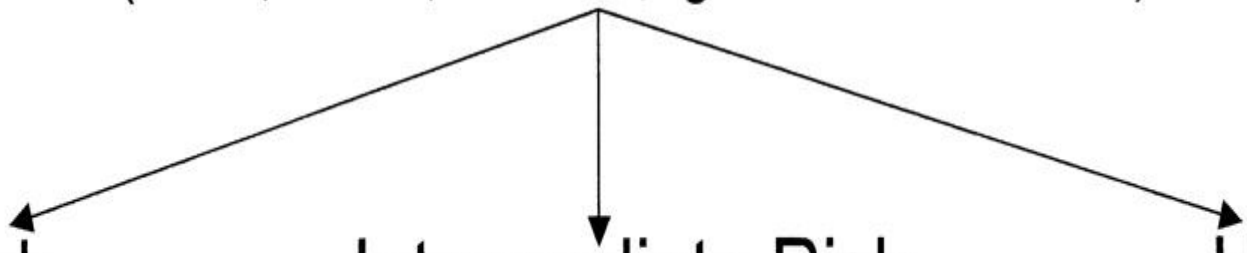
- **Oblimersen – bcl2-directed antisense oligonucleotide**
- **Lenalidomide**
- **Flavopiridol**
- **Anti-CD23**
- **Anti-CD40**

Vaccine strategies

Supportive therapy (allopurinol, G-CSF, blood and platelet transfusion, immunoglobulins, antibiotics)

Categorize According to Risk

(FISH, CD38, ZAP-70, Ig mutational status)



Low Risk

Minimally toxic therapy

- Rituximab
- Chlorambucil
- Fludarabine

Intermediate Risk

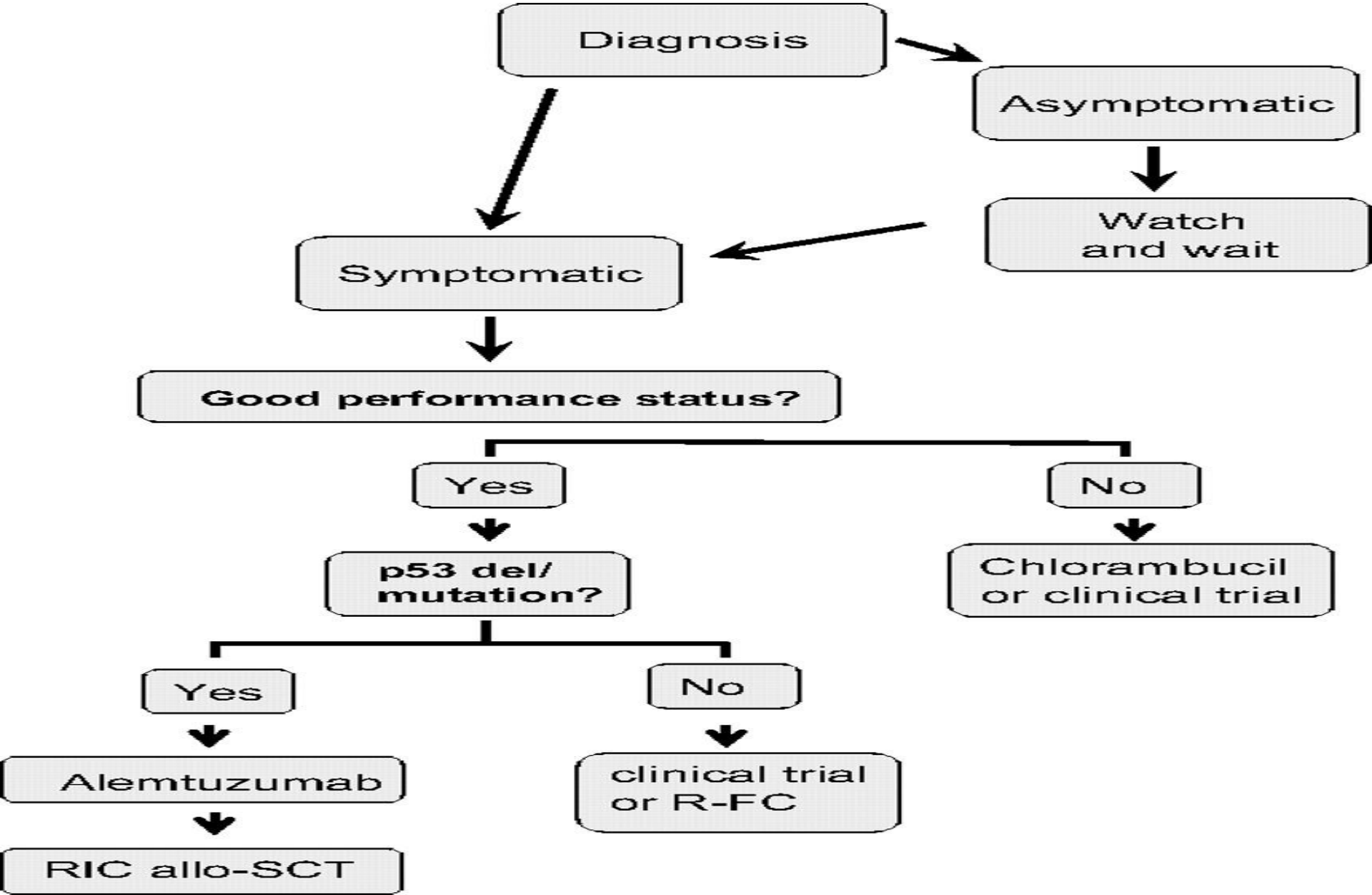
Nucleoside analog combination regimens

- Fludarabine and cyclophosphamide
- Fludarabine and rituximab
- Fludarabine, cyclophosphamide, and rituximab

High Risk

- Clinical trial
- BMT, myeloablative or non-myeloablative

CLL – TREATMENT STRATEGY



CLL - COMPLICATIONS

Severe systemic infections

Bleeding

Richter's transformation

Prolymphocytoid transformation

Secondary malignancies

Acute myeloid leukemia

DIFFERENTIAL DIAGNOSIS

A) With malignant well-differentiated lymphocytic lymphoma (LS): chronic lymphocytic leukemia is diagnosed, which after a few years represent an exacerbation of evolution

B) With Waldenstrom macroglobulinemia. From this disease it is necessary to differentiate very rare cases of chronic lymphocytic leukemia

C) With the disease of heavy chains such as gamma (Franklin's disease). From this entity it is necessary to differentiate cases of chronic lymphocytic leukemia with low lymphocytosis