Chronic Lymphocytic Leukemia
accumulation of mature-appearing lymphocytes in the blood, marrow, lymph nodes, and spleen.
CLL cells are:

monoclonal B lymphocytes
that express CD19, CD5, and CD23

weak or no expression
of surface immunoglobulin (Ig), CD20, CD79b, and FMC7
incidence of CLL varies throughout the world, highest in North America and rare in the Far East
The disease is rare in young people

the incidence rises in the fourth decade and continues to rise exponentially

mean age at diagnosis being 69.6 years and >80% of patients being >60 years
PATHOPHYSIOLOGY
Predisposing Factors

no firm evidence linking an occupational exposure

infection in the etiology of this disease?

family history of CLL or another lymphoproliferative disorder is a strong risk factor for CLL
1 in 10 patients with CLL has a family history of CLL or another lymphoproliferative disorder.

30-fold increase in the risk of CLL in first-degree relatives of patients with CLL.

13 to 18% of first-degree relatives have a peripheral blood CD5+ monoclonal B-cell lymphocytosis.
Patients with familial CLL are -10 years younger than those with sporadic CLL.

Anticipation may occur in familial CLL with affected children being 15 to 20 years younger than their parents at diagnosis.
There is no consistency in the clinical features of affected members with familial CLL.
the CLL cell is a memory B cell

two forms of CLL

- Pre-germinal lymphocyte and lacking mutations of the \textit{IgVH} gene
- Other having traversed the germinal center and containing mutations
Abnormalities in Apoptosis

defect in apoptosis typifies CLL with the majority of cells being long-lived Non cycling and in Go

there is a small fraction of replicating cells in the lymph nodes and marrow that is responsible for disease progression
Genomic Abnormalities

Conventional cytogenetic proved difficult because CLL cells have a very low proliferative index

clonal chromosomal abnormalities are detected in -50% of cases
Analysis by Conventional Cytogenetic

The most common clonal abnormality was trisomy 12 (36%)

structural abnormalities of chromosome 13 (20%)

structural abnormalities of chromosome 14 (16%)
The 13q abnormalities usually involved a 13q14 deletion (site of the \textit{Rb} gene)
patients with abnormal karyotyping had a worse prognosis than those with normal cytogenetic,

trisomy 12 was usually seen in those 15% of cases with CLL variants, (CLL /PLL) or "atypical" CLL
those with chromosome 14 abnormalities had the worst prognosis

11q22-q23 deletion have been detected in 13% of patients

these patients had disease progression and poor survival
Analysis by Fluorescence in Situ Hybridization

most present-day studies use FISH to identify and quantify the genetic defects in CLL

Evaluation of 325 CLL patients for deletions of 6q21, 11q22-q23, 13q14, and 17p13;
268 (82%) had abnormalities

deletion 13q14 being most frequent (55%)

deletion 11q22-q23 (18%)

trisomy 12q13 (16%), deletion 17p13 (7%)

deletion 6q21 (7%)
The median survival times

17 p deletion $\rightarrow$ 32 months

11q22-q23 deletion $\rightarrow$ 79 months

trisomy 12q $\rightarrow$ 114 months

normal karyotype $\rightarrow$ 111 months

13q deletion $\rightarrow$ 133 months
deletion 13q as the only abnormality had similar survival to those with normal chromosomes

only one third required therapy
Patient with 17p13 or 11q22-q23 deletions

Have the poorest survival, more marked lymphadenopathy splenomegaly, and are more likely to be symptomatic with night sweats and weight loss.
correlation between genomic abnormalities and presence of IgV/II gene mutations and alterations in cell morphology
<table>
<thead>
<tr>
<th>Genomic Abnormality</th>
<th>Classical Cytogenetics&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Fluorescence in Situ Hybridization&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Affected Genes</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>50&lt;sup&gt;c&lt;/sup&gt;</td>
<td>18</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>13q deletion</td>
<td>10</td>
<td>55</td>
<td><em>Rb, MiR-15a, MiR-16-1</em></td>
<td>Good prognosis</td>
</tr>
<tr>
<td>11q deletion</td>
<td>8</td>
<td>18</td>
<td><em>ATM</em></td>
<td>Younger; bulky lymphadenopathy; poor prognosis</td>
</tr>
<tr>
<td>12q trisomy</td>
<td>13</td>
<td>16</td>
<td><em>mdm2</em></td>
<td>“Atypical” morphology; end-stage disease</td>
</tr>
<tr>
<td>17p deletion</td>
<td>4</td>
<td>7</td>
<td><em>P53</em></td>
<td>CLL/PLL morphology; drug resistance; very poor prognosis</td>
</tr>
<tr>
<td>6q deletion</td>
<td>4</td>
<td>6</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
Clonal Evolution

additional chromosomal abnormalities develop with disease progression

16 to 39% incidence of new or additional chromosomal abnormalities, which develop over several years from initial diagnosis
By FISH analysis, one quarter of patients will have the development of new abnormalities after 5 years particularly in patients who are ZAP-70-positive, CD38 positive, and those with unmutated IgVH
patients with un mutated IgVH have an increased risk of developing deletions of 11q22-q23 or 17p13,

those with mutated IgVH develop deletions of 13q
treatment with fludarabine increases the expression of p53-dependent genes, increasing the risk of selecting out 17p13-deleted cells.

42% of fludarabine-resistant CLL patients have either p53 mutations or deletions.
CLINICAL FINDINGS
most CLL patients are elderly

-10% of patients are <50 years old

the presenting features are similar regardless of age

70 to 80% of patients are diagnosed incidentally and they have early-stage
The most frequent complaint is fatigue or a vague sense of being unwell.

Less frequently:

enlarged nodes or the development of an infection is the initial complaint.
Fever and weight loss are uncommon at presentation but may occur with advanced and drug-resistant disease.
Enlargement of the cervical and supraclavicular nodes occurs more frequently than axillary or inguinal lymphadenopathy

mild to moderate enlargement of the spleen

splenic infarction is uncommon
Less common manifestations:

- enlargement of the tonsils
- abdominal masses due to mesenteric or retroperitoneal lymphadenopathy
- skin infiltration.
Anemia: related to marrow replacement or autoimmune hemolysis and aplasia

bruising or bleeding secondary to:

thrombocytopenia, acquired von Willebrand disease, or an acquired inhibitor to factor VIII
paraneoplastic syndrome

nephrotic syndrome, paraneoplastic pemphigus, or angioedema
LABORATORY FINDINGS
Peripheral Blood

The median lymphocyte count at diagnosis is 30000 /mL,

in most patients there is a continuous increase in the lymphocyte count over time
In half >12 months for the lymphocyte count to double
cyclic fluctuations of up to $50 \times 10^9$/L can occur in the lymphocyte counts of untreated patients in others, the count may remain stable for years.
CLL-cells:

normal small to medium-sized lymphocytes

clumped chromatin

inconspicuous nucleoli

small ring of
cytoplasm
Smudge cells are commonly seen

Appear to be caused by a decrease in vimentin

Relationship between ~30% smudge cells
And mutated IgVH and better prognosis than
French/American/British classification

Classical CLL: are small >90% of cells

the cells are **CLL/PLL**: when 11 to 54% of e pro lymphocytes

atypical **CLL**: >15% of the lymphocytes are plasmoid or cleaved and <10% are prolymphocytes

prolymphocytic leukemia: ~55% of the cells are pro lymphocytes,
There is always strong proliferation of the typical small lymphocytes, which are usually spread out diffusely.
densely structured nuclei and little variation in CLL cells

small cytoplasmic layer
Slightly eccentric enlargement of the cytoplasm in the lymphoplasmacytoid variant of CLL
large lymphocytes with irregularly structured nucleus, well-defined nucleolus, and wide cytoplasm (transitional form CLL/PLL)
Prolymphocytic leukemia of the T-cell series (T-PLL) with indented nuclei and nucleoli
Bone Marrow

There are four patterns of marrow involvement in CLL

Interstitial
Nodular: the least common
Mixed: most common

Diffuse: effacement of the fat spaces by tumor, carries the worst prognosis
Immunophenotyping

leukemic cells have the B-cell markers

Cd19, Cd20 (low), Cd43, Cd79b (low), and, by definition, must be Cd5+

weak expression of slgM and slgD

Cd23+ and Cd10 –

These cells are also Cd27+:
Suggesting that these cells are memory B cells
Recommendation for the use of five markers to differentiate CLL from other B-cell malignancies

Typical CLL should be:

- surface Ig (weak)
- Cd5+, Cd23+
- Cd79b or Cd22 (weak)
- FMC7
membrane Cd23 over expression is an activation marker may play a role in the decreased apoptosis observed in this disease is useful to differentiate CLL from mantle cell lymphoma
FMC7 is usually strongly expressed in hairy cell leukemia and prolymphocytic leukemia,

16% of CLL cases also stain positively those patients who are FMC7+ have high levels of Surface IgM, low expression of Cd23, and poor prognosis
The Cd 5 antigen is most commonly associated with mature T cells and is expressed weakly on thymocytes.

Normal B cells carrying the CD 5 marker are located in the mantle zone of the lymph node, and in the peripheral blood.
The Cd5 molecule has been
appears to be involved in the activation of T lymphocytes

function of Cd5 on the B cell remains unknown
studies suggested that 5% of cases of CLL could be Cd5-

These cases were more likely to be FMC7+, Cd23-, Cd11b+, and Cd13+ and had a poor prognosis.
<table>
<thead>
<tr>
<th>Marker</th>
<th>Marker Intensity</th>
<th>Score</th>
<th>Marker Intensity</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface Immunoglobulin</td>
<td>Weak</td>
<td>1</td>
<td>Strong</td>
<td>0</td>
</tr>
<tr>
<td>CD5</td>
<td>+</td>
<td>1</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>CD23</td>
<td>+</td>
<td>1</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>CD22/CD79b</td>
<td>Weak</td>
<td>1</td>
<td>Strong</td>
<td>0</td>
</tr>
<tr>
<td>FMC7</td>
<td>-</td>
<td>1</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

+, present; -, absent.

NOTE: Diagnosis of chronic lymphocytic leukemia requires a score of 4 or 5.
A score of 4 or 5 had an accuracy of 97 percent for the diagnosis of CLL, while most of the other non-CLL B-cell lymph proliferative diseases had scores of zero to two.
<table>
<thead>
<tr>
<th>Condition</th>
<th>smIg</th>
<th>CD5</th>
<th>CD10</th>
<th>CD11c</th>
<th>CD19</th>
<th>CD20</th>
<th>CD22</th>
<th>CD23</th>
<th>CD25</th>
<th>CD43</th>
<th>CD79b</th>
<th>CD103'</th>
<th>FMC7</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>Dim</td>
<td>++</td>
<td>–</td>
<td>–/+</td>
<td>++</td>
<td>Dim</td>
<td>–/+</td>
<td>++</td>
<td>+/-</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–/+</td>
</tr>
<tr>
<td>Waldenström macroglobulinemia</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–/+</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>–/+</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>+</td>
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<tr>
<td>Prolymphocytic leukemia</td>
<td>+++</td>
<td>–/+</td>
<td>–/+</td>
<td>–/+</td>
<td>++</td>
<td>+++</td>
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<td>HCL</td>
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<td>HCL variant</td>
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<td>–</td>
<td>+</td>
<td>++</td>
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<td>+++</td>
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<tr>
<td>Splenic lymphoma with villous lymphocytes</td>
<td>++</td>
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<td>–/+</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Marginal zone lymphomas</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>+/–</td>
<td>++</td>
<td>++</td>
<td>+/–</td>
<td>+/–</td>
<td>–</td>
<td>–/–</td>
<td>++</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>++</td>
<td>++</td>
<td>–/+</td>
<td>–</td>
<td>++</td>
<td>++</td>
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<td>–</td>
<td>+</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>++</td>
<td>–/+</td>
<td>++</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>–/+</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>++</td>
</tr>
</tbody>
</table>
Approximately 50% of patients had >30% Cd38+ cells, and these patients had un mutated IgVh and had a worse prognosis than those with <30% Cd38+ cells.
Cd 38 acts as a receptor and enzyme and can produce cell replication and survival with a variety of signals.

Activation of Cd38+ cells, through slgM induces apoptosis and through IgD prolongs cell survival and induces differentiation.
Cd38 can be measured easily by flow cytometry

disagreement about the number of cells that are required to define positivity, with values ranging from 5 to 30%

Moreover, the number of Cd38-positive cells can vary over time
ZAP-70 is a member of the Syk-ZAP-70 protein kinase family

is expressed in T and natural killer cells

Is important in T-cell signaling

recent evidence suggests that normal B-cells may also express ZAP-70, particularly when activated
Gene expression studies in CLL have demonstrated that cells with unmutated IgVu have increased expression of ZAP-70.

70 to 90% correlation between ZAP-70 expression and IgVh mutational status, whether ZAP-70 was measured by flow cytometry (>20% cells positive), Western blot analysis, or immunohistochemistry.
ZAP-70 positivity correlates the presence of poor-risk cytogenetic, del llq22-q23, del and trisomy 12 and del 17 P13

unlike Cd38, the ZAP-70 status appears stable over time
Functional Immune Abnormalities

80% of patients have recurrent infections

sepsis being the major cause of death
CLL patients are susceptible to:

typical bacterial infections

opportunistic infections, particularly if they have received nucleoside analogs or monoclonal antibodies
hypogammaglobulinemia is the major cause of infection.

CLL patients also have abnormalities in T cells, complement, and neutrophil function.
Hypogammaglobulinemia and agammaglobulinemia

- The severity increases with the duration and stage of disease
- The Ig levels are all decreased
- Within the IgG class, reduced levels of IgG2 and IgG4 correlate best with the risk of infection
- The decline in IgA levels is the most important predictor of infection
pathogenesis of the hypogammaglobulinemia:

- impaired B-cell function
- regulatory abnormalities of T cells
- suppress Ig secretion by normal B cells in vitro by CLL-derived natural killer (NK) cells
inversion of the T-helper to T-suppressor cell ratio

increase in the number of T-suppressor cells may correlate with the degree of hypogammaglobulinemia

decreased T-helper function

abnormality in the large granular lymphocyte population
levels of different complement components are decreased

multiple defects in neutrophil function have been described
Autoimmune Manifestations

CLL is the most common cause of autoimmune hemolytic anemia, causing 14% of cases.

4 to 25% of CLL patients develop AIHA with a warm-type antibody against the Rhesus system.
the incidence is higher in:

Men, lymphocyte > 60000 and >60 years old
Immune thrombocytopenia (ITP) occurs in 2% of patients.

The diagnosis is based on an increase in platelet size in the PBS and an increase in megakaryocytes in the marrow.

Approximately one third of these patients with ITP have a positive Coombs test.
Whether autoimmune neutropenia occurs in CLL is unclear

Pure red cell aplasia occurs in ~1% of cases and may be caused by a T-cell mechanism
Nephrotic syndrome related to membranous or membranoproliferative

acquired angioedema

autoimmune blistering skin diseases
DIAGNOSIS
peripheral blood lymphocyte count >5 x 10⁹

<55% of the cells being atypical

Bcell specific differentiation antigens (CD19, CD20, and CD23) and be CD5+

bone marrow aspirate showing >30% lymphocytes
INVESTIGATIONS AND STAGING
investigations

complete blood count, review of the peripheral smear, and immunophenotyping are required for diagnosis
A marrow aspirate/biopsy is not required for diagnosis but may be useful under the following circumstances:

to establish the cause of anemia and thrombocytopenia for patients with Rai stage III or IV disease

To confirm that there is no paratrabecular localization or cyclin D1 staining in atypical cases

To assess the pattern of marrow infiltration, which is of prognostic value

To assess response following chemotherapy
reticulocyte count

Coombs test, renal and liver function tests LDH, serum protein electrophoresis and/or immunoelectrophoresis, and Ig levels.

The plasma B-microglobulin level

as this is a simple and important prognostic marker and an indicator of response to therapy
A baseline chest radiograph

computed tomograph (CT) scans of the chest and abdomen will depend on clinical indications

Positron emission tomography (PET) scans are not useful for staging in CLL

Before starting chemotherapy
screen for active viral infections (hepatitis Band C, cytomegalovirus)
Staging

The Rai staging system is generally used in North America
### Rai System\(^a\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Risk Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis, lymphocytes in blood (&gt; 15,000/mcL) and (&gt; 40%) lymphocytes in the bone marrow</td>
<td>Good</td>
</tr>
<tr>
<td>I</td>
<td>Stage 0 with enlarged node(s)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>II</td>
<td>Stage 0-I with splenomegaly, hepatomegaly, or both</td>
<td>Intermediate</td>
</tr>
<tr>
<td>III(^c)</td>
<td>Stage 0-II with hemoglobin (&lt; 11.0 \text{ g/dL}) or hematocrit (&lt; 33%)</td>
<td>High</td>
</tr>
<tr>
<td>IV(^c)</td>
<td>Stage 0-III with platelets (&lt; 100,000/mcL)</td>
<td>High</td>
</tr>
</tbody>
</table>

### Binet System\(^b\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Hemoglobin (\geq 10 \text{ g/dL}) and Platelets (\geq 100,000/\text{mm}^3) and (&lt; 3) enlarged areas</td>
</tr>
<tr>
<td>B</td>
<td>Hemoglobin (\geq 10 \text{ g/dL}) and Platelets (\geq 100,000/\text{mm}^3) and (\geq 3) enlarged areas</td>
</tr>
<tr>
<td>C(^c)</td>
<td>Hemoglobin (&lt; 10 \text{ g/dL}) and/or Platelets (&lt; 100,000/\text{mm}^3) and any number of enlarged areas</td>
</tr>
<tr>
<td>Rai Stage at Diagnosis</td>
<td>Percent of Patients Never Requiring Chronic Lymphocytic Leukemia Therapy</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>O. Lymphocytosis $&gt;5 \times 10^3/L$ only</td>
<td>59</td>
</tr>
<tr>
<td>1. Lymph node (LN) enlargement</td>
<td>21</td>
</tr>
<tr>
<td>2. Spleen/liver (S/L) enlargement ± LN</td>
<td>23</td>
</tr>
<tr>
<td>3. (Anemia with hemoglobin $&lt;11 \text{ g/dL}$) ± LN or S/L</td>
<td>5</td>
</tr>
<tr>
<td>4. (Thrombocytopenia $&lt;100 \times 10^{12}/L$ ± LN or S/L)</td>
<td>0</td>
</tr>
</tbody>
</table>
several points should be made
The staging is based on clinical examination and not on CT scans

patients with autoimmune cytopenia have a better prognosis than patients with cytopenia related to marrow packing

The diagnosis of CLL was originally based on typical cell morphology peripherallymphocytosis
PROGNOSIS
Rai and Binet Staging

the median survival
of patients with stage A disease or in the low-risk group is > 10 years

40% of these patients will progress to a more advanced disease
50% of patients will require therapy at some point
25% will die from their disease
Age and Sex

10% of CLL patients are <50 years old

clinical features and staging at presentation are similar to those > 50 years

the proportion of deaths that can be attributed directly to CLL is greater for the younger age group
The male-to-female ratio for CLL is 2:1

women are more likely to have early-stage disease
women have a better prognosis than men
an increased incidence of IgVH mutated disease

good prognostic genetic markers in women

hormonal differences
lymphocyte Characteristics

Morphology: 20% of patients have atypical CLL or CLL/PLL more advanced stage.

- a higher proliferative index
- trisomy 12 or deletion of 17p13 (p53 mutation).
- CD38+

aberrant cell morphology: an independent prognostic marker

patients with >30% smudge cells have a better prognosis than with <30% smudge cells
Number
Survival decreases with increasing lymphocyte count

median survival is 8.6 years for a lymphocyte count <20000

3.7 years if the count is >40000
Doubling Time

patients with a lymphocyte doubling time of <12 months have a significantly worse survival rate
Immune Markers

increase in surface lgs , FMC7+, or increased intensity of CD20

associated with atypical morphology trisomy 12 and poor prognosis
CD38+ has been associated with:

- shorter survival
- correlates with increasing Rai stage.
- intrathoracic and abdominal lymphadenopathy
- short doubling time
- increased B2-microglobulin levels
- atypical morphology
- the CD38 status is useful to predict which patients within a particular clinical stage will progress
ZAP-70

70 to 90% correlation between ZAp-70 expression and absence of IgVH mutations

ZAP-70 positivity correlates moderately with CD38 positivity and the presence of poor-risk cytogenetics

The median survivals for ZAP-70-positive and ZAP-70-negative patients are 9.3 and 24.4 years
Molecular Genetics and Cytogenetics
**p53, Ataxia Telangiectasia Mutation, Retinoblastoma**

Mutations of p53: in 10 to 15% of patients predictive of resistance to CTx

The abnormality is associated with aberrant cell morphology and very poor survival

ATM and Rb protein levels are reduced in 34 and 42% of patients

these patients have advanced-stage disease and reduced survival
Marrow Histology

Nodular growth patterns: 90 months

interstitial growth patterns: 46 months

diffuse infiltration: median survival time of only 28 months

Fibrosis of the marrow indicates an aggressive clinical course
The pattern of marrow involvement after chemotherapy is also prognostically important:

nodular partial remission:

persistent leukemia and have a shorter time to relapse compared to those in complete remission
Fludarabine Resistance

Patients who do not respond to fludarabine or who relapse within 6 months of treatment have a median survival of 10 months with standard chemotherapy.
Serum Markers

Elevated B2microglobulin:

predict resistance to chemotherapy

Increased levels of LDH  B2-microglobulin
CD23 , and TNF-a:

patients who are at risk of disease progression.
TREATMENT

one third of CLL patients never require therapy,

one third need treatment as soon as they are seen,

one third have disease progression over the years and require therapy at some point
With the possible exception of allogeneic hematopoietic cell transplantation (HCT), CLL cannot be cured by current treatment options. Immediate versus delayed treatment strategies: no improvement in long-term survival with early treatment.
<table>
<thead>
<tr>
<th>Indications to Treat in CLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 or greater fatigue limiting life activities</td>
</tr>
<tr>
<td>B-symptoms persisting for 2 weeks or greater</td>
</tr>
<tr>
<td>Lymph nodes greater than 10 cm or progressively enlarging lymph nodes causing symptoms</td>
</tr>
<tr>
<td>Spleen or liver with progressive enlargement or causing symptoms</td>
</tr>
<tr>
<td>Anemia (Hemoglobin &lt;11 g/dL) referable to CLL</td>
</tr>
<tr>
<td>Thrombocytopenia (Platelets &lt;100 × 10^12/L) referable to CLL</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura poorly responsive to traditional therapy</td>
</tr>
<tr>
<td>WBC &gt; 300 × 10^9/L on two occasions two weeks apart if no alternative comorbid diseases increase morbidity of Treatment</td>
</tr>
<tr>
<td>Severe paraneoplastic (insect hypersensitivity, vasculitis, myositis, etc) process related to CLL not responsive to traditional therapies</td>
</tr>
</tbody>
</table>
Response Criteria and Minimal Residual Disease (MRD)
### RESPONSE DEFINITION AFTER TREATMENT FOR CLL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Complete response</th>
<th>Partial response</th>
<th>Progressive Disease</th>
<th>Stable Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy(^b)</td>
<td>None above 1.0 cm</td>
<td>Decrease ≥ 50%</td>
<td>Increase ≥ 50%</td>
<td>Change from -49% to +49%</td>
</tr>
<tr>
<td>Liver and/or spleen size</td>
<td>Normal size</td>
<td>Decrease ≥ 50%</td>
<td>Increase ≥ 50%</td>
<td>Change from -49% to +49%</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>None</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>&gt; 1500/mm(^3)</td>
<td>&gt; 1500/mm(^3) or</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 50% improvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulating B lymphocytes</td>
<td>Normal</td>
<td>Decrease ≥ 50% over</td>
<td>Increase ≥ 50%</td>
<td>Change from -49% to +49%</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&gt; 100,000/mm(^3)</td>
<td>&gt; 100,000/mm(^3) or</td>
<td>Decrease ≥ 50% over</td>
<td>Change from -49% to +49%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>increase ≥ 50% over</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&gt; 11.0 g/dL (untransfused)</td>
<td>&gt; 2 g/dL from baseline</td>
<td>Decrease of &gt; 2 g/dL from baseline</td>
<td>Increase &lt; 11.0 g/dL or &lt; 50% over baseline, or decrease &lt; 2 g/dL</td>
</tr>
<tr>
<td>Marrow</td>
<td>Nomocellular, &lt; 30% lymphocytes, no B-lymphoid nodules</td>
<td>Hypocellular, or ≥ 30% lymphocytes, or B-lymphoid nodules, or not done</td>
<td>Increase of lymphocytes to more than 30% from normal</td>
<td>No change of marrow infiltrate</td>
</tr>
</tbody>
</table>
MRD

estimated that 25% of patients with a CR criteria will have MRD-positive disease

same prognosis as those in PR?

patients who achieve a marrow MRD-negative CR will have sustained remissions and perhaps improved survival
two-color (CD19/CD5) flowcytometry to detect MRD, with a sensitivity of one CLL cell in $1 \times 10^{-2}$ leukocytes

four-color (CD19/CD5/CD20/CD79b) flowcytometry can detect one CLL cell in $5 \times 10^{-5}$ leukocytes

new four-color (CD81/CD22/ CD19/CD5) flowcytometry assay
ongoing studies are required to develop a simple and reproducible assay for MRD that can be used universally

more intense treatments to achieve an MRD-negative Marrow?
Treatment options include purine analogs, alkylating agents, monoclonal antibodies, and combinations of these agents.