Chronic Lymphocytic Leukemia (CLL) — Staging and Prognosis

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Chronic lymphocytic leukemia (CLL) affects the B-cells of the immune system and is, as the most common leukemia in adults, an important hematological differential diagnosis. It often hardly progresses for years and therefore a CLL does not always need immediate therapy. In the past years especially, a lot has happened with regard to diagnostic options and treatment, so that being informed about cytogenetic diagnostics and new treatment methods is extremely important.

Definition of CLL

Chronic Lymphocytic Leukemia as the Most Common Type of Leukemia

The chronic lymphocytic leukemia (CLL) is the most common type of leukemia and belongs, being a leukemic B-cell-lymphoma, to the group of low grade, indolent non-Hodgkin lymphomas. Clonal proliferation of the usually non-immunocompetent B-cells induces an accumulation in the bone marrow, the spleen and lymph nodes and causes a leukocytosis in the peripheral blood.
The disease usually becomes manifest at a higher age and shows a slow progress of symptoms, so that initially a therapy often may be disclaimed.

Today lymphocytic proliferative leukemia, which originates from T-cells, is not called T-CLL anymore. This disease is named **T-cell prolymphocytic leukemia** and often presents a severe progression.

### Epidemiology of CLL

#### CLL Especially Affects Men of a Higher Age

CLL, having an incidence of 4 per 100,000/year, is the most common of all types of leukemia. Age distribution of the disease's onset shows a clearly increasing incidence at higher ages. The mean age at the point of diagnosis is about 70 years and men are affected more often than women.

### Etiology of CLL

#### Probable Causes of Chronic Lymphocytic Leukemia

The exact etiology of CLL remains unexplained to this day. A known risk factor is, among older age, a positive family history. Furthermore, organic solvents are discussed as a trigger.

### Pathophysiology of CLL

#### The Role of B-lymphocytes in the Development of Chronic Lymphocytic Leukemia

[Diagram showing the cells CLL affects](https://creativecommons.org/licenses/by-sa/4.0) by Cancer Research UK. License: CC BY-SA 4.0
Chronic lymphocytic leukemia is based on an uncontrolled proliferation of mature B-lymphocytes. Generally, this population of B-lymphocytes is monoclonal, which means that it is made up of identical copies of a single B-lymphocyte.

Moreover, in the case of CLL, all cells appear mature, small and in good order, but they do not fulfill an immunological function. If these B-cell lymphoma cells reach the peripheral blood, it is referred to as a leukemic washout.

If the clonal B-cells are, for example, limited to a lymph node area, it is referred to as small cell lymphocytic lymphoma if it is consisting of the same type of cells.

In the course of the disease, the proliferating population of lymphoma cells also further increases in the bone marrow and extrudes other cell types, which explains the lack of erythrocytes (anemia), thrombocytes (thrombocytopenia) and functioning B-lymphocytes (antibody deficiency syndrome).

Clinical Symptoms of CLL

Chronic Lymphocytic Leukemia as a Common Incidental Finding

CLL, as a slowly progressing disease of elderly people, often is an incidental finding in the investigation of a leukocytosis at hand; thus, almost 50% of the patients are free of symptoms at the point of diagnosis.

Early signs are general symptoms like fatigue, tiredness and performance dip, as well as classical signs of b symptoms. They involve the triad of night sweats, fever of unknown origin (FUO) and unintended loss of weight.

In the further course, a majority of the patients develops an enlargement of lymph nodes, a lymphadenopathy that typically has a dense consistency and is indolent; moreover, an enlarged spleen (splenomegaly) or liver (hepatomegaly) is found quite often.

CLL can also become apparent on the skin in the form of pruritus, chronic urticarial, mycosis and herpes zoster. Such dermatological symptoms in older patients should always let oneself keep in mind a possible CLL. The rare Mikulicz-syndrome in CLL-patients denotes a swelling of the parotic gland and the lacrimal gland.

A common and dangerous complication is the antibody deficiency syndrome. Clonal CLL-cells displace the functional B-cell population and increase the risk of infections this way significantly. A reduced amount of granulocytes (neutropenia) advantages bacterial infections. This is a major cause of death of this type of leukemia.

Other complications are an autoimmune hemolytic anemia (AIHA), an autoimmune thrombocytopenia and a secondary transition into a highly malignant lymphoma. The last phenomenon is called Richter's transformation, which comes with a worse prognosis.

Diagnosis of CLL
Blood Count Gives Information about the Chronic Lymphocytic Leukemia

In the diagnostic investigation of the CLL, the first suspicion is made by often an accidental finding of a leukocytosis. In the subsequent differential blood count, typically, an increased percentage of lymphocytes are found, usually between 70 to 95%.

In blood smears of CLL-diseased, there are often found Gumprecht shadows, which come off destructed leukocytes. This, however, are to a lesser extent specific and also appear in long-stored blood samples, so that significance for a safe positive diagnosis is rather low.

Bone marrow cytology is not necessarily required for diagnosis, but can support a suspect of CLL in cases with a percentage of 30% or more mature lymphocytes among all nucleated cells.

The mature lymphocytes of the CLL are analyzed by using flow cytometry regarding their immunophenotype. The expression of the B-CLL surface proteins CD19, CD20 and CD23 with simultaneous expression of the T-cell antigen CD5 is characteristic for a leukemic population of lymphocytes.

The clonally proliferated B-cells can also be accounted for the often diagnosed light chain restriction of either kappa- or lambda-light chains.

To assure the diagnoses, the following criteria of the IWCLL (International Workshop of Chronic Lymphocytic Leukemia) from 2008 must be fulfilled:

- More than 5,000 clonal B-lymphocytes/µL in the peripheral blood
- Predominantly small, mature looking lymphocytes in cytological diagnostics
- Expression of the B-cell antigens CD19, CD20, CD23 and the T-cell antigen CD5
- Light chain restriction to provide evidence for monoclonality

Note: If there are now symptoms and less than 5,000 B-lymphocytes/µL in the peripheral blood, it is referred to as a monoclonal B-cell-lymphocytosis (MBL), which can proceed into a manifest CLL. Diseased patients are examined periodically, since this may provide decisive predications about their prognosis. Over 80% of the patients present with genetic transformations in the analysis. One of the most common mutations is a deletion 13q14 and comes with good prognosis. However, patients having a
deletion 17p13 are usually hit decisively harder. In the later course of the disease, increasing consequences of the expulsion caused by clonal B-cells can be observed. The lack of healthy B-lymphocytes induces an antibody deficiency in the serum; an expulsion in the bone marrow can result in a detectable anemia or thrombocytopenia.

Staging of Chronic Lymphocytic Leukemia

![Image: “Splenomegaly in a CLL Patient” by Hellerhoff. License: CC BY-SA 3.0](image)

For staging the disease, a few other examinations are required. A splenomegaly or hepatomegaly can be detected with the aid of sonography.

Clinical examination of lymph nodes is as well extremely important. If a leukemic manifestation is not found, like it is the case of the small cell lymphocytic lymphoma whose cytology is identical to the CLL, a biopsy of enlarged lymph nodes might be indicated. It is also performed to rule out a Richter's transformation.

**Note:** The small cell lymphocytic lymphoma equals a CLL without a leukemic washout into the peripheral blood.

If all results are on hand, the disease is classified into clinical stages by either the Binet- or the Rai-staging system to evaluate prognosis and the best possibly therapy this way. Both of the two staging systems are still in clinical use.

### Binet Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>Lymphocytosis and less than 3 affected lymphoid areas</td>
</tr>
<tr>
<td>B</td>
<td>Lymphocytosis and 3 or more affected lymphoid areas</td>
</tr>
<tr>
<td>C</td>
<td>Anemia (Hb &lt; 10 g/dL) or thrombocytopenia (thrombocytes &lt; 100/nl)</td>
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### Rai Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis</td>
</tr>
<tr>
<td>I</td>
<td>Stage 0 plus lymphadenopathy</td>
</tr>
<tr>
<td>II</td>
<td>Stage I plus hepatomegaly and/or splenomegaly</td>
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<tr>
<td>Stage III</td>
<td>Stage II plus anemia (Hb &lt; 11g/dL)</td>
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<tr>
<td>Stage IV</td>
<td>Stage III plus thrombocytopenia (&lt;100.000/µL)</td>
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**Differential Diagnosis**

![Image: "Restricted expression of Bcl-2 within the lymphocytes in chronic lymphocytic leukemia in contrast to malignant melanoma cells" by Openi. License: CC BY 2.0](image)

**Important Differentiation Concerning Chronic Lymphocytic Leukemia**

The most important differential diagnosis, including a relevant lymphocytosis, is the **monoclonal B-lymphocytosis (MBL)** which seems similar to the phenotype of CLL in over 80% of the cases with a number of lymphocytes of less than 5,000/µL.

Moreover, other lymphomas which can present with leukemic progression, i.e. the **mantle cell lymphoma**, must be kept in mind. A **chronic myeloid leukemia (CML)** should be ruled out by cytogenetic examinations. Regions of enlarged lymph nodes should be examined histologically for clarification of other possible causes.

**Treatment of CLL**

**A Patient’s Age is Often Essential for the Type of Therapy in CLL**

Up to now, there is now curative therapy for chronic lymphocytic leukemia besides allogenic stem cell transplantation. Since the disease is usually progressing slowly, therapy often is not necessary at times of diagnosis (**watch and wait**). The respectively used therapy record is arranged regarding:

- The disease’s stage
- The patient’s age and general condition
- The patient’s wish

Younger patients and such in better general condition rather tolerate aggressive chemotherapy than weak patients, which possibly would not profit from cytostatic therapy anymore.
Changes in the Therapy of Chronic Lymphocytic Leukemia

The past years have brought tremendous changes in the therapy of CLL. Especially, there are an increasing number of options available which complement conventional chemotherapy, or even replace it. Generally, an indication for therapy is aligned regarding symptomatology, so that a lymphocytosis by itself does not present a reason for medicinal treatment, but this dogma also could be questioned by the application of early therapy free of chemotherapeutic substances (stage Binet A).

As first-line therapy, the **FCR-regimen** is applied in patients in good general condition and especially young patients. Thereby, **Fludarabin** out of the group of purine analogs is combined with **cyclophosphamide** out of the group of alkylating agents and **Rituximab**, a CD20-antibody.

Studies have demonstrated that new generations of CD20-antibodies like Ofatumumab and especially Obinutuzumab yield better results after treatment.

The CD52-antibody **Alemtuzumab** is used in a subgroup of CLL having a worse prognosis due to a **deletion 17p13**, since here sensitivity to chemotherapeutics is generally worse and a clearly better result in terms of a progression-free survival (PFS) has been proven.

Patients having a reduced general condition or organic dysfunctions are primarily treated with **chlorambucil** or **bendamustine**. Both substances are alkylating agents with fewer side effects like granulocyto- or thrombocytopenia. Bendamustine is also combined with Rituximab according to the **BR-regimen**.

A relapse therapy, the choice of a proper therapy, is clearly more variable. A relapse after 2 years is often treated by repeating first-line therapy. Depending on the patient’s condition and the genetic and immuno-phenotypical type of CLL, alternative types of therapies are planned.

Newer substances are i.e. the BTK-inhibitor **Ibrutinib** and the PI3-kinase-inhibitor **Idealisib**. The CD52-antibody **Alemtuzumab** is also used for monotherapy. A new future approach could be effectuated by blocking the BCL-2 protein, since the corresponding substance **ABT-199** has yielded promising results in clinical trials.
Furthermore, in cases of therapy refractory CLL or high-risk patients, **allogenic stem cell transplantation** comes into consideration, which, however, is likewise associated with a high mortality risk.

### Additional Therapeutic Measures

The therapeutic concept is completed by applying demand-actuated treatments, which corresponds to the progression of the disease. Immunosuppressed CLL-patients should receive periodic **vaccination** to prevent infections with influenza or pneumococci. An antibody deficiency can be treated by substituting **immunoglobulins**.

Large lymphomas can be treated with low-dose **radiation** and autoimmune phenomena can be treated with **glucocorticoids** in acute situations.

### Progression and Prognosis of CLL

#### Cytogenetics as a Progress Determining Factor of CLL

Prognosis of a diagnosed chronic lymphocytic leukemia is significantly depending on the disease’s stage and cytogenetics. Progress can be at a minimum level for years, so that a lifelong “watch and wait” strategy can be maintained. Likewise, an aggressively proceeding form can progress into death quickly. The median survival of CLL that has been diagnosed in stage Binet A is above 10 years, in stage C below 3 years.

### Review Questions

The answers are below the references.

1. **Chronic lymphatic leukemia**...
   
   A. ...belongs to the B-cell neoplasms.
   B. ...is, according to the FAB-classification, a myelodysplastic syndrome.
   C. ...belongs to diffuse large B-cell lymphomas.
   D. ...belongs to the myeloproliferative diseases.
   E. ...is a rare disease among the diseases with leukemic progression.

2. **Which chromosomal change is associated with a poor prognosis of CLL?**
   
   A. Trisomy 12q
   B. Deletion 13q14
   C. Trisomy 21
   D. Deletion 17p13
   E. Partial monosomy 5p.

3. **Which of the named phenomena is not a typical complication of CLL?**
   
   A. Antibody deficiency syndrome
   B. Anemia
   C. Transition into a highly malignant, diffuse B-cell lymphoma
   D. Severe bacterial infections
   E. Myeloic blast crisis
References


**Correct answers:** 1A, 2D, 3E

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