Chronic Lymphocytic Leukemia (CLL) — Staging and Prognosis

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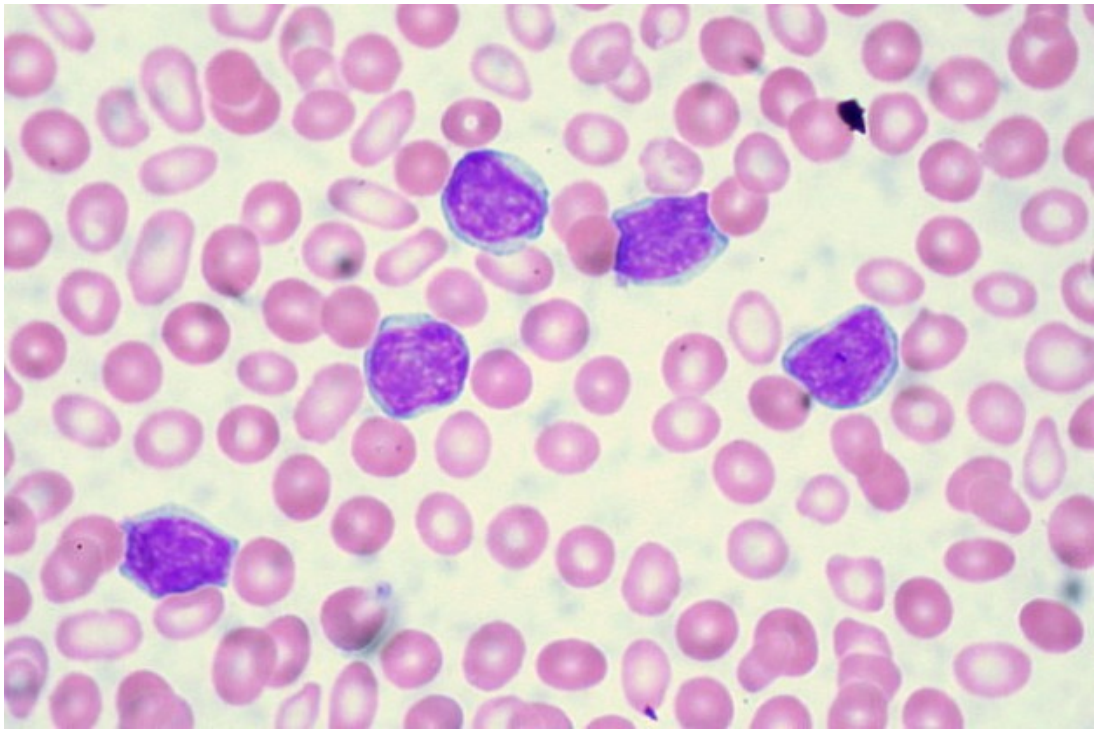
Chronic lymphocytic leukemia (CLL) affects the B-cells of the immune system and is, as the most common leukemia in adults, an important hematological differential diagnosis. It often hardly progresses for years and therefore a CLL does not always need immediate therapy. In the past years especially, 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 Chronic Lymphocytic Leukemia

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 accumulation in the bone marrow, the spleen, and lymph nodes, and causes leukocytosis in the peripheral blood.

The disease usually becomes manifest at a higher age and shows a slow progression 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 onset of the disease shows an 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 CLL

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

Pathophysiology of CLL

The role of B lymphocytes in the development of CLL

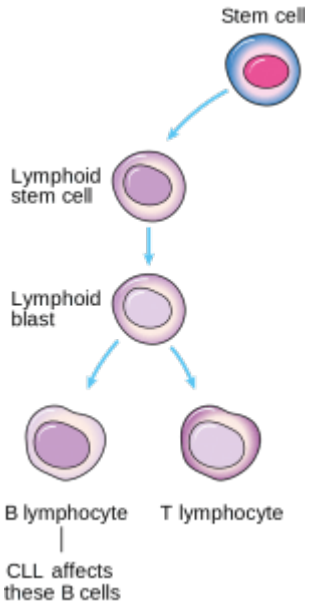


Image: Diagram showing the cells CLL affects. By Cancer Research UK, License: CC BY-SA 4.0

CLL 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, e.g., limited to a lymph node area, it is referred to as **small cell lymphocytic lymphoma** if it consists 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

CLL is a common incidental finding

CLL, a slowly progressing disease of elderly people, is often 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 develop an **enlargement of lymph nodes**, 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 be indicative of a possible CLL. The rare **Mikulicz-syndrome** in CLL patients denotes a swelling of the parotid gland and the lacrimal gland.

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

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

Diagnosis of CLL

Blood count gives information about the CLL

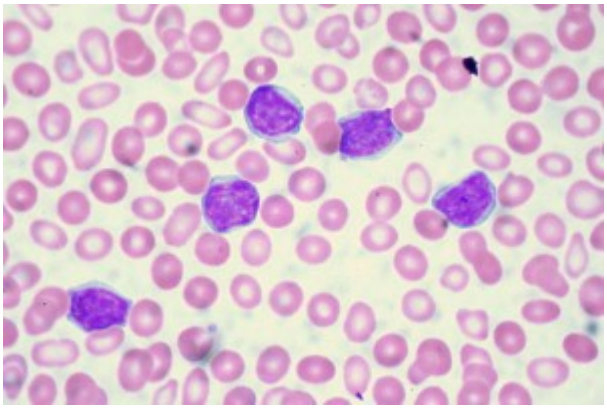


Image: Peripheral blood film from a 70-year-old woman with an absolute lymphocyte count of 41,000/uL. By Ed Uthman, License: CC BY-SA 2.0

In the diagnostic investigation of the CLL, the 1st suspicion is often made by an accidental finding of a **leukocytosis**. In the subsequent differential blood count, typically, an increased percentage of lymphocytes are found, usually between 70–95%.

In blood smears of CLL-diseased, often **Gumprecht shadows are found**, which come off the destroyed leukocytes. These, 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 the diagnosis but can support a suspicion 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 for 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 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 predictions 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 a good prognosis. However, patients having a **deletion 17p13** are usually hit decisively harder.
In the later course of the disease, increasing the 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

detectable **anemia** or **thrombocytopenia**.

Staging of CLL

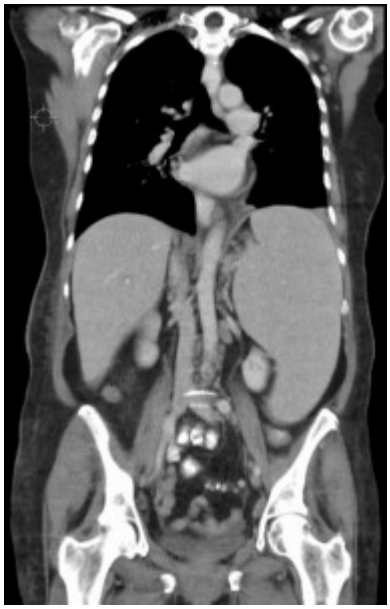


Image: Splenomegaly in a CLL Patient. By Hellerhoff, License: CC BY-SA 3.0

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

Clinical examination of lymph nodes is extremely important. If a leukemic manifestation is not found like it is in 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 possible therapy this way. Both the staging systems are still in clinical use.

Binet staging system

Stage A	Lymphocytosis and less than 3 affected lymphoid areas
Stage B	Lymphocytosis and 3 or more affected lymphoid areas
Stage C	Anemia (Hb < 10 g/dL) or thrombocytopenia (thrombocytes < 100/nL)

Rai staging system

Stage 0	Lymphocytosis
Stage 1	Stage 0 plus lymphadenopathy
Stage 2	Stage 1 plus hepatomegaly and/or splenomegaly
Stage 3	Stage 2 plus anemia (Hb < 11g/dL)
Stage 4	Stage 3 plus thrombocytopenia (< 100,000/µL)

Differential Diagnosis

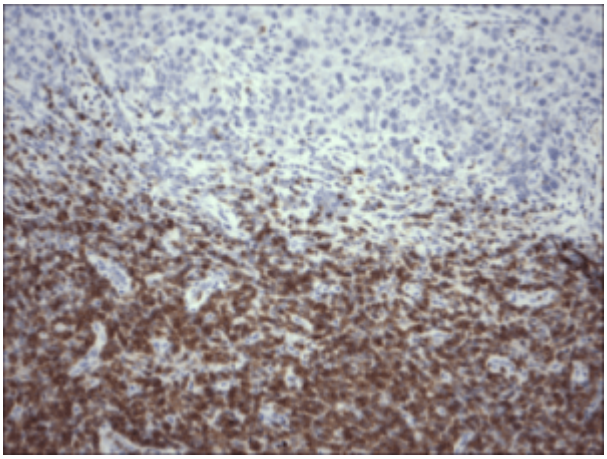


Image: Restricted expression of Bcl-2 within the lymphocytes in chronic lymphocytic leukemia in contrast to malignant melanoma cells. By Openi, License: CC BY 2.0

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 several lymphocytes of less than 5,000/µL.

Moreover, other lymphomas that can present with leukemic progression, i.e. the **mantle cell lymphoma**, must be kept in mind. **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

There is a curative therapy for CLL besides allogeneic stem cell transplantation. Since the disease progresses slowly, therapy often is not necessary at times of diagnosis (**watch and wait**). The respectively used therapy record is arranged based on:

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

Changes in the therapy of CLL

The past years have brought tremendous changes in the therapy of CLL. There is an increasing number of options available which complement conventional chemotherapy or even replace it. Generally, an indication for therapy is aligned with 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).

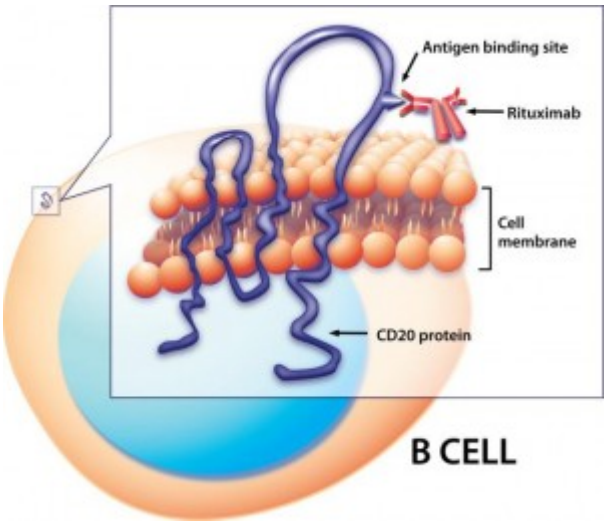


Image: Computer-generated illustration of rituximab binding to CD20 protein on B cell. By NIAID, License: CC BY 2.0

As 1st-line therapy, the **FCR-regimen** is applied in patients in good general condition, especially young patients. Thereby, in the group of purine analogs, f**ludarabine** is combined with **cyclophosphamide** in the group of alkylating agents, and r**ituximab**, a CD20-antibody.

Studies have demonstrated that new generations of CD20-antibodies like ofatumumab and especially obinutuzumab yield better results after the treatment.

The CD52-antibody a**lemtuzumab** is used in a subgroup of CLL and has a poor prognosis due to a **deletion 17p13;** sensitivity to chemotherapeutics is generally worse and a better result in terms of 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 granulocytosis or thrombocytopenia. Bendamustine is also combined with rituximab according to the **BR-regimen.**

Relapse therapy, the therapy of choice, is more variable. Relapse after 2 years is often treated by repeating 1st-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 include the BTK-inhibitor i**brutinib** and the PI3-kinase-inhibitor i**delalisib**. The CD52-antibody a**lemtuzumab** is also used for monotherapy. New future approaches could be explored 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, **allogeneic stem cell transplantation** comes into consideration, which, however, is likewise associated with high mortality risk.

Additional therapeutic measures

The therapeutic concept is completed by applying demand-actuated treatments, which correspond to the progression of the disease. Immunosuppressed CLL-patients should

receive periodic **vaccination** to prevent infections with influenza or pneumococci. 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 progress determining factor of CLL

The prognosis of diagnosed CLL significantly depends on the stage of the disease and cytogenetics. Progress can be at a minimum level for years so that a lifelong ‘watch and wait’ strategy can be maintained. Likewise, aggressive forms of CLL can progress rather quickly. The median survival of patients diagnosed with stage Binet A is greater than 10 years, while those diagnosed with stage Binet C has a median survival of fewer than 3 years.

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Notes