Journal of Current Hematology & Oncology Research

Review

DOI: 10.51271/JCHOR-0014

Chronic lymphocytic leukemia

Kemal Fidan

Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Erciyes University, Kayseri, Turkey

Cite this article: Fidan K. Chronic lymphocytic leukemia. *J Curr Hematol Oncol Res.* 2023;1(3):59-67.

Corresponding Author: Kemal Fidan, drkemalfidan@hotmail.com

Received: 17/07/2023 ◆ **Accepted**: 26/07/2023 ◆ **Published**: 30/08/2023

ABSTRACT

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a mature B-cell neoplasm characterized by progressive accumulation of monoclonal B lymphocytes. CLL is considered being identical to SLL. Malignant cells seen in CLL and SLL have the same pathological and immunophenotypic features. The term CLL is used when the disease occurs mainly in the blood, while the term SLL is used when the involvement is mainly nodal.

Keywords: Chronic lymphocytic leukemia, small lymphocytic lymphoma, mature B-cell neoplasm

CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a mature B-cell neoplasm characterized by progressive accumulation of monoclonal B lymphocytes.

CLL is considered being identical to SLL. Malignant cells seen in CLL and SLL have the same pathological and immunophenotypic features. The term CLL is used when the disease occurs mainly in the blood, while the term SLL is used when the involvement is mainly nodal.

EPIDEMIOLOGY

CLL constitutes approximately 25-35% of all leukemias. It is the most common leukemia among adults in Western countries.[1] It manifests as SLL, primarily in the lymph nodes, in less than 10% of patients. CLL/SLL is more common in men, with a male/female ratio of approximately 1.2:1 to 1.7:1.[1,2] Worldwide, there are approximately 191,000 cases of CLL/SLL per year, as well as 61,000 deaths from the disease.[3]

The median age of diagnosis of CLL/SLL is approximately 70 years. Although it is rare to occur before the age of 40, the incidence of the disease increases logarithmically after the age of 45. The incidence of CLL/SLL varies by race and geographic location. In the United States, there is a higher incidence among White Americans compared to African Americans or Asian Pacific Islanders.[4] It is extremely low in Asian countries such as China and Japan.[5,6]

ETIOLOGY

There are no clearly discernable occupational or environmental risk factors that predispose to CLL/SLL. The role of radiation and chemotherapy in the development of CLL has not been proven. Exposure to chemicals, such as solvents, benzene, dyes, and pesticides, is not a proven risk factor for CLL. Compared to other leukemias, familial occurrence is most prominent in CLL. Multiple CLL cases were observed at a higher frequency in a single family. Close to 10% of CLL patients have a relative with 1st or 2nd degree CLL. Although the majority of CLL cases precede monoclonal B-cell lymphocytosis (MBL), a small percentage of these people develop CLL. In addition, polymorphisms in CD5 (localized on chromosome 11q23), CD38 (localized in chromosome 4p15), the gene encoding TNF-alpha, and other genes mapping chromosome 13q21,33q22.2 are genetic factors that cause an increase in the incidence of CLL.

PATHOGENESIS

The pathogenesis of CLL/SLL is a complex process leading to the accumulation of monoclonal, mature, dysfunctional B lymphocytes in peripheral blood, bone marrow, lymph nodes, and spleen (**Figure 1**).

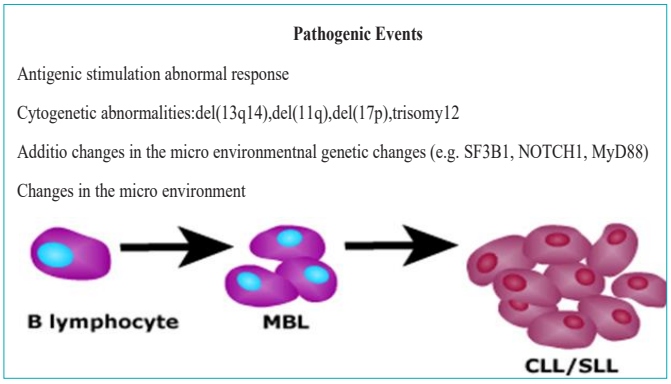

Figure 1. Pathogenesis of CLL-SLL

The pathogenesis of CLL/SLL is complex but appears to follow a two-stage pattern of progression. First, MBL develops as a result of genetic changes that are thought to be the product of an abnormal response to antigenic stimulation. A secondary event, occurring randomly rather than cumulative damage, causes tumor cells to accumulate and progress to CLL/SLL. Signs and symptoms (hepatomegaly, splenomegaly, cytopenia, infection, lymphadenopathy) are associated with the accumulation of functionally dysfunctional lymphocytes in the bone marrow, lymph nodes, and other organs.

CLINICAL SYMPTOMS

Symptoms

Most patients are diagnosed with an absolute lymphocytosis during a routine blood count without any symptoms. Others are diagnosed with painless swelling in the lymph nodes, which usually grow and shrink spontaneously in the cervical region, but do not disappear completely, after examinations made during the visit to the doctor.

5-10% of patients may have B symptoms including one or more.[7] These are;

- Weight loss of 10% of body weight in the last six months
- Fever >38°C for ≥2 weeks without evidence of infection
- Night sweats without signs of infection
- Extreme tiredness (not able to work or do normal daily activities)

Findings

Lymphadenopathy: It is the most common abnormal finding detected on physical examination and is seen in approximately 50-90% of patients.[8-9] Patients may present with localized LAP as well as with diffuse LAP. The cervical, supraclavicular, and axillary lymph nodes are most commonly affected. Characteristically, the lymph nodes are painless, firm, round, and mobile with palpation. Sometimes, lymph nodes in the same anatomical region may merge (conglomerated LAP) to form large lymphoid masses.

Splenomegaly: Spleen enlargement is seen in 25-55% of cases.[8,9] It is the second most enlarged organ after lymph nodes. The enlarged spleen is usually painless and has a smooth surface with a sharp, hard edge on palpation.

Hepatomegaly: Liver size is detected in 15-25% of cases at the time of diagnosis.[8,9] It is usually 2-6 cm palpable from the right costal margin and is approximately 10-16 cm. On palpation, it is usually not sensitive and has a smooth surface.

Skin and other organ involvement: CLL/SLL lymph nodes can also be seen outside of the liver and spleen. The skin is probably the most frequently involved non-lymphoid organ for ease of examination. Skin lesions (leukemia cutis) are mostly seen in the face region and may present as macules, papules, plaques, nodules, ulcers, or vesicles.[10] Diagnosis can be made by skin biopsy. Skin involvement occurs in less than 5% of cases and may not significantly affect prognosis unless biopsy shows Richter's transformation.

Unlike other lymphomas, gastrointestinal mucosal involvement is rare. At the same time, although meningeal leukemia is very rare, its incidence varies between 0.2-2%.[11] Paraneoplastic renal involvement forms such as membranoproliferative glomerulonephritis (MPGN), minimal change disease, and amyloidosis can also be seen rarely.[12]

LABORATORY

Lymphocytosis

The most important laboratory abnormality in CLL is B-cell lymphocytosis in the peripheral blood and bone marrow. The absolute blood lymphocyte threshold for the diagnosis of CLL is >5000/microL ($5x10^9$/L) (12). A significant proportion of lone patients present with a lymphocyte count as high as 100,000/microL ($100x10^9$/L).

Sometimes excessive lymphocytosis may cause complications due to increased hyperviscosity (e.g. transient ischemic attack, stroke).[13] However, there is no clear consensus on this threshold value. Particular attention should be paid to patients with other risk factors for cerebrovascular complications (e.g., hypertension, atherosclerotic disease) and hydration should be offered to these patients.

Cytopenias

Although not severe at the time of initial diagnosis, neutropenia, anemia and thrombocytopenia may be seen. In addition, autoimmune hemolytic anemia (AIHA), pure red cell aplasia (pure red cell aplasia, PRCA), autoimmune thrombocytopenia (ITP) and agranulocytosis may contribute to the development of cytopenia. The incidence of autoimmune hemolyticanemia is increased in patients with CLL. Direct Coombs (antiglobulin) test (DAT) positivity can be seen during the disease in approximately 35% of cases. Overt AIHA occurs in approximately 10% of cases and is usually later in the course of the disease.[14] Pure red cell aplasia occurs in approximately 0.5 percent of patients. Unlike AIHA, PRCA can occur early in CLL. Immune Thrombocytopenia (ITP) is seen in 2-3% of patients with CLL and may be the first finding that may be an indication for treatment.[14] Agranulocytosis can be seen very rarely at 0.5%.

Immunoglobulin Abnormalities

Hypogammaglobulinemia is present in approximately 25% of patients at the time of diagnosis, and up to two-thirds of patients may develop it later in the course of the disease.[15] Usually, all three immunoglobulin classes (IgG, IgA, and IgM) are reduced, but in some patients only one or two is low. CLL patients are more susceptible to major bacterial infections when low immunoglobulin levels and neutropenia are present. Polyclonal increases in gamma globulins are seen in approximately 15% of patients.

Abnormal Biochemical Findings

Approximately 60% of patients with progressive or advanced CLL have increased levels of lactate dehydrogenase (LDH) and beta-2 microglobulin. Elevations in uric acid, hepatic enzymes (ALT or AST) and, rarely, calcium may also be observed.

PATHOLOGICAL CHARACTERISTICS

Peripheral Smear

Lymphocytosis is seen in the peripheral blood smear of patients with CLL. Typically, most leukemic cells are mature-appearing lymphocytes with narrow basophilic cytoplasm, dense nuclei, no nucleoli (**Figure 2**). Occasionally, some of the circulating cells are composed of medium-sized prolymphocytes with large or oval notched nuclei and prominent, single, central nucleoli, usually constituting

a small fraction of the lymphocyte population. Also, the peripheral smear often contains "basket" cells (basket cells). These are lymphocytes that are mechanically disintegrated in the process of spreading onto the lamella, probably because CLL cells are more fragile than normal lymphocytes.[16]

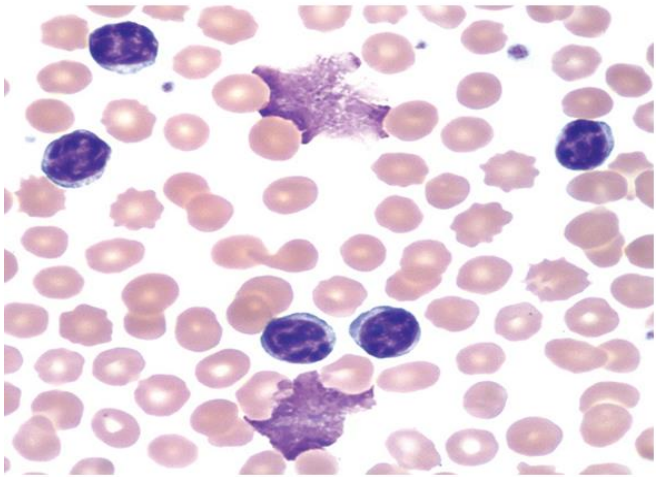

Figure 2. Chronic lymphocytic leukemia peripheral blood smear

Immunophenotype

Immunophenotypic analysis, usually performed by flow cytometry, is a key component in the diagnosis of CLL.[17] CLL cells carry CD5, except for B lymphocyte surface markers (CD19, CD20, CD23). Surface immunoglobulin (SmIg), FMC7, CD22 and CD79b are expressed lower than in either negative or normal B lymphocytes. Typically, only a single immunoglobulin light chain (kappa or lambda) is expressed. In addition, CLL cells are cyclin D1 and CD 10 (usually) negative. CD38 (>30%) is expressed in approximately 40% of cases.

BONE MARROW ASPIRATION AND BIOPSY

Bone marrow aspiration and biopsy are not required for the diagnosis of CLL. If bone marrow biopsy and aspiration are performed at initial diagnosis, they usually show normal to increased cellularity, with lymphocytes accounting for >30% of all nucleated cells. The bone marrow involvement pattern may be interstitial, nodular or diffuse (**Figure 3**).

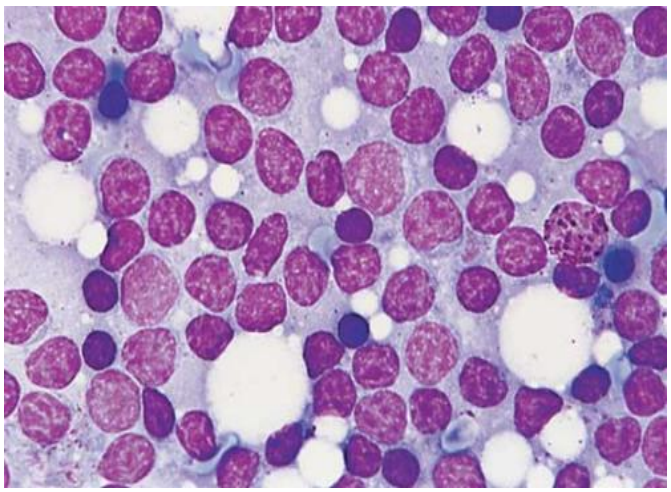

Figure 3. Diffuse involvement of the bone marrow by lymphocytes

Lymph node and spleen histology

The structure of involved lymph nodes is diffusely deleted, sometimes with scattered residual bare germinal centers. The lymph node infiltrate consists predominantly of small lymphocytes with dense chromatin, round nuclei and rarely a small nucleolus.[18] Larger lymphoid cells (prolymphocytes and paraimmunoblasts) with more prominent nucleoli and scattered chromatin are often present. These large lymphoid cells are usually collected in “pseudofollicles” (**Figure 4**). This condition is considered pathognomonic for CLL/SLL. In the spleen, it usually shows both white and red pulp infiltration, but white pulp involvement is usually more prominent.

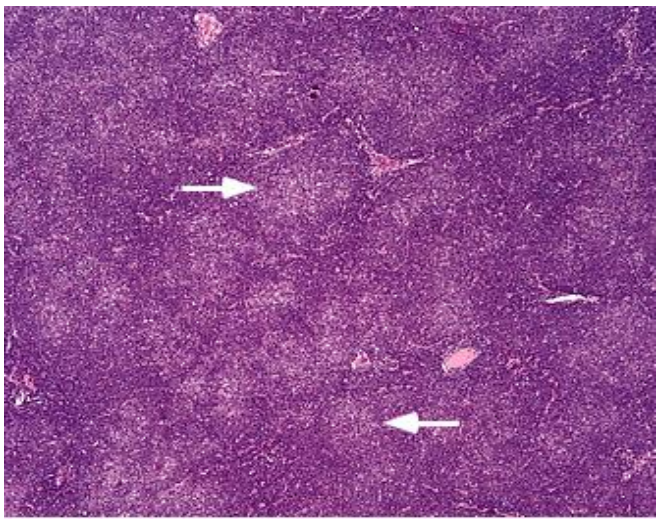

Figure 4. Lymph node biopsy in a patient with CLL

EVALUATION AND DIAGNOSIS

CLL is suspected in a patient presenting with an absolute lymphocytosis. Complete blood count, peripheral smear and flow cytometry should be requested for the evaluation of these patients. Bone marrow is usually not required but may be performed for the evaluation of patients with unexplained cytopenia. In contrast, the diagnosis of SLL usually involves painless swelling of the lymph nodes in the adult, usually in the cervical region, which can enlarge and shrink spontaneously, but does not disappear completely. Evaluation of such patients typically requires a tru-cut or excisional biopsy of a lymph node. For extranodal regions, biopsy of the relevant tissues and bone marrow biopsy and aspiration are performed in those with cytopenia. Regardless of the absolute lymphocyte count in the peripheral blood or the presence of lymphadenopathy, the demonstration of typical CLL cells in the bone marrow in the case of any cytopenia makes the diagnosis of CLL. In addition, SLL is diagnosed in patients with nodal, spleen or extramedullary involvement and no bone marrow involvement.

For the diagnosis of CLL, both of the following criteria must be met, according to the 2018 CLL National Cancer Institute guidelines.

- In peripheral blood; Absolute B lymphocyte count ≥5000/micro/L (5 x 10^9/L), which is determined to be at least 3 months and morphologically mature small lymphocytes predominate in the peripheral smear,
- In peripheral blood flow cytometry; low SmIg levels, presence of B-cell associated antigens (CD19, CD20 and CD23), demonstration of CD5 and immunoglobulin light chain (kappa or lambda) positivity.

DIFFERENTIAL DIAGNOSIS

The diagnosis of CLL is suspected when the peripheral blood in an adult shows an absolute lymphocytosis. However, lymphocytosis can occur in non-neoplastic conditions such as viral or other infections (e.g., infectious mononucleosis, pertussis, toxoplasmosis) as well as in neoplastic conditions other than CLL (e.g., leukemic phase of lymphomas, hairy cell leukemia). Therefore, for differential diagnosis; first, to distinguish between reactive causes of lymphocytosis and clonal (malignant) causes, and second, to distinguish CLL from other malignant lymphoproliferative diseases. A clear diagnosis of CLL can be made in a patient with peripheral blood lymphocytosis and a CLL immunophenotype on flow cytometry (**Table 1**).

The differential diagnosis of patients presenting with lymphadenopathy and without minimal or no lymphocytosis includes other lymphoid malignancies. In this case, the most reliable morphological distinction is the presence of proliferation centers in the relevant lymph nodes of SLL and the absence of other pathological findings. CLL/SLL may also develop into an aggressive histology (Richter transformation), which may sometimes be present at the time of diagnosis.

Causes of Lymphocytosis

1.Infections: In case of infection (such as infectious mononucleosis, pertussis, toxoplasmosis), transient lymphocytosis can be seen in the peripheral blood of patients.

For a diagnosis of CLL to be made, lymphocytosis must last longer than 3 months. Unlike CLL, lymphocytosis due to infectious causes is not clonal, does not show the characteristic immunophenotype of CLL, and does not infiltrate the bone marrow.

In addition, atypical lymphocytes (T lymphocytes) are observed in viral infections.

2.Monoclonal B-cell lymphocytosis (MBL): Monoclonal B-cell lymphocytosis (MBL) is used for an absolute increase in the number of clonal B lymphocytes in the peripheral blood not exceeding 5000/microL (5 x 10^9 /L) in the absence of other signs of disease (e.g., lymphadenopathy, organomegaly, cytopenia).

3.Prolymphocytic leukemia (PLL): Prolymphocytes that differ from typical CLL cells are present in the peripheral smear or bone marrow. Compared to CLL cells, these are medium to large sized cells with vesicular nuclear chromatin, a prominent nucleoli, and moderate amounts of cytoplasm that appear somewhat immature. In PLL of B lymphocyte origin (B-PLL), prolymphocytes are of the B lineage, expressing glossy surface membrane immunoglobulin (SmIg) and generally not CD5 (**Table 1**).

4.Mantle cell lymphoma (MCL): MCL cells also express CD5 and CD20 together (Table 1). Also, in the vast majority of cases, MCL cells stain strongly for cyclin D1, express high levels of SmIg and CD20, have t(11;14) chromosomal aberration, and are negative for CD23. In contrast, CLL cells are negative for cyclin D1 and often CD23 positive.

5.Lymphoplasmacytic lymphoma (LPL): Both LPL and SLL are lymphoproliferative disorders that usually progress slowly. LPL is synonymous with Waldenström macroglobulinemia, a hyperviscosity syndrome caused by high serum IgM levels. A minority of cases are CD5 positive and show increased monoclonal paraprotein. LPL can be distinguished from CLL by the absence of CD23 expression, the presence of strong staining for surface IgM and CD20, and the presence of cytoplasmic Ig (**Table 1**).

6.Hairy cell leukemia (HCL): HCL and CLL/SLL may be associated with high lymphocyte counts in peripheral blood, but leukocytosis in HCL is much less common and occurs in only about 10-20% of cases. HCL often presents with splenomegaly and cytopenia but almost never involves lymph nodes, whereas lymphadenopathy is almost always found in CLL/SLL. The diagnosis of HCL is often suspected based on the presence of circulating lymphocytes (hairy cells) with cytoplasmic projections (65). Classical forms of HCL are distinguished from CLL based on immunophenotypic findings such as "bright" staining for CD20 and surface immunoglobulin, positivity for CD25, CD11c, annexin A1 and CD103, and an inability to express CD5 in the majority of cases (**Table 1**).

7.Follicular lymphoma (FL): Follicular lymphoma (FL) patients, similar to CLL/SLL patients, may present with diffuse painless peripheral lymphadenopathy, often in a cascade over long periods of time. Both have small tumor cells. FL can be distinguished from CLL/SLL by immunophenotype. Unlike FL, tumor cells in CLL do not express CD10; in contrast, tumor cells in FL, unlike CLL, do not express CD5 (**Table 1**).

8.Splenic marginal zone lymphoma (SMZL): Both SMZL and CLL can present with splenomegaly and peripheral blood lymphocytosis. Also, both CLL and SMZL can express CD23, CD43, CD5 and IgD, although their expression is much more typical for CLL. Unlike CLL, SMZL may have bright SmIg and CD20 (**Table 1**). In difficult cases, pathological evaluation of the bone marrow, spleen and lymph nodes may be required to establish the diagnosis.

Table 1.Classical immunophenotype of low-grade lymphoproliferative diseases

	CD5	CD19	CD20	CD23	CD10	CD25	CD103	CD200	sIg
CLL	+	+	slightly glossy	+	-	+/-	-	+	slightly glossy
MCL	+/-	+	glossy	-/dim	-	+/-	-	-	glossy
FL	-	+	+	+/-	+	-	-	-	+
MZL	+/-	+	glossy	+/-	-	+/-	-	-	+/glossy
HCL	-	glossy	glossy	-	-	+	+	+	+
WM/LPL	+/-	+	+	+/-	+/-	+/-	-	+	+/variable
B-PLL	-	+	glossy	+/-	-	-	-	+/-	glossy

PROGNOSIS AND STAGING

Prognosis

The natural history of CLL/SLL is highly variable, with a survival time of approximately 2-20 years from initial diagnosis. Some patients experience rapid deterioration and die within 2-3 years from complications or from causes directly related to CLL/SLL. Other's progress clinically well for 5-10 years, followed by a terminal phase lasting 1-2 years. A small proportion (<30%) of patients have a good clinical course for 10-20 years and the ultimate cause of death may be unrelated to CLL/SLL. Spontaneous clinical regression has been reported very rarely in the absence of treatment.[19] In the asymptomatic stage, patients continue their daily lives, but in the advanced stage, the performance status is impaired due to repeated hospitalizations. The most common causes of death are due to severe systemic infection (especially pneumonia and septicemia), bleeding, cachexia and disease-related complications.

Staging

The Rai and Binet staging systems divide patients into 3 risk groups based on predicted overall survival (OS) (**Table 2**, **3**). Survival curves for Rai low risk (stage 0), intermediate risk (stage I or II), and high risk (stage III or IV) groups correspond to Binet grades A, B and C, respectively. Advanced stage is associated with shorter survival.

Treatment of CLL has improved markedly in recent years. Therefore, the prognosis has improved with the advent of new treatments.[20] The advanced stage causes deterioration of bone marrow function (anemia and thrombocytopenia), beginning in the blood and bone marrow (lymphocytosis), involving the lymph nodes (lymphadenopathy), spleen and liver (organomegaly). Over time, patients tend to progress from an early stage (low risk), to an intermediate stage, and eventually to an advanced stage (high risk). Imaging is not used for routine staging but should be performed in patients with enlarged abdomen or pelvic LAP related signs or symptoms. Cytopenias may be due to bone marrow involvement or may be due to autoimmune causes (such as AIHA, ITP). According to retrospective studies, patients with cytopenia due to autoimmune processes have a better prognosis than patients with cytopenia due to bone marrow failure.[21]

Rai Staging System

The Rai staging system uses physical examination and complete blood count to classify patients into 3 risk groups (**Table 2**). While the prognostic value of the Rai and Binet grading system continued, the estimated median AS increased significantly as treatments improved.

Binet Staging System

The Binet staging system uses physical examination and complete blood count to classify patients into 3 risk groups with different estimated AS (**Table 3**). To determine Binet stage, physical examination evaluates 5 potential sites of lymphoid involvement (cervical, axillary, and inguinal lymph nodes unilateral or bilateral, each area counted as one), spleen, and liver. Lymph node enlargement is defined as ≥1 cm.

In addition to Rai and Binet, genetic prognostic factors that can determine the prognosis, especially in the early stage, are also used in staging (**Table 4**). The patient group with 17p deletion has the worst prognosis with a mean survival of 2 years.[22] Although another bad prognostic factor is 11q deletion, this bad risk effect has been overcome with treatments such as FCR (fludarabine, cyclophosphamide, rituximab). The unmutated immunoglobulin heavy chain variable region gene (immunoglobulin variable heavy chain (IGHV)) also indicates the possibility of high-risk disease.

In addition to these two clinical and laboratory-based classifications, a new classification system, which includes genetic data, has started to come into use. In this new classification, which is called chronic lymphocytic leukemia-International Prognostic Index (CLL-IPI), 5 independent prognostic factors are used (**Table 5**).[23] The risk groups evaluated in 4 different categories according to this system and their survival percentages are shown in **Table 6**.

Table 2. RAI staging system

Stage	Risk	Explanation	Average survival (months)
0	Low	Absolute lymphocytosis in peripheral blood or bone marrow (>5000/mm3)	>150
I	Mild	Lymphocytosis and lymphadenopathy	101
II	Mild	Lymphocytosis and hepatomegaly and/or splenomegaly ± lymphadenopathy	71
III	High	Lymphocytosis and anemia (Hgb<11 g/dl) (and/orsplenomegaly, hepatomegaly, lymphadenopathy)	19
IV	High	Lymphocytosis and thrombocytopenia (platelet count <100,000/microL (and/or anemia, splenomegaly, hepatomegaly, lymphadenopathy)	19

Table 3. Binet staging system

Stage	Risk	Explanation	Average survival (months)
A	Low	<3 lymphatic region involvement	could not be reached
B	Mild	≥3 lymphatic region involvement (Hgb≥10gr/dl, platelet count≥100.000/mm^3)	84
C	High	Hgb<10gr/dl, platelet count<100,000/mm3 (number of areas with lymph node involvement is not important)	24

Table 4. Genetic risk factors	
Genetic marker	**Risk group**
Del 17p and/or p53 mutation	High risk
Del 11q	Medium-high risk
Del 13 q	Low risk
Trisomy 12	Medium risk
NOTCH1 mutation	Medium-high risk
SF3B1 mutation	Medium-high risk
BIRC3 mutation	High risk

Table 5. Chronic lymphocytic leukemia international prognostic index (CLL-IPI)	
Age	**≤65:0 point** **>65:1 point**
Clinical stage	Binet A/Rai 0: 0 point Binet B, C/Rai I-IV: 1 point
B2 microglobulin (mg/L)	≤3.5:0 point >3.5:1 point
IGHV mutation	Yes:0 point None: 2 point
Del 17p and/or p53 mutation	Yes:4 point None: 0 point
≥7 points: very high risk 4-6 points: high risk 2-3 points: medium risk ≤1 point: low risk	
CLL-IPI score	**5-year overall survival (%)**
Low risk	93.2
Medium risk	79.3
High risk	63.3
Very high risk	23.3

Table 6. Risk groups and survival rates according to the chronic lymphocytic leukemia international prognostic index (CLL-IPI)	
CLL-IPI score	**5-year overall survival (%)**
Low risk	93.2
Medium risk	79.3
High risk	63.3
Very high risk	23.3

TREATMENT IN CLL

Not all patients with CLL need treatment at the time of diagnosis. The main reasons for this are; Similar treatment outcomes of CLL between the normal population and certain patient subgroups, with the exception of allogeneic hematopoietic stem cell transplantation (AHSCT), the inability to cure CLL with current treatment options, no improvement in long-term survival with early treatment in patients treated early or late. Cannot be displayed.[24-25]

Pre-treatment Evaluation

History and physical examination,

Questioning systemic symptoms (fever, night sweats, weight loss, malaise)

Complete Blood Count and Peripheral Blood Smear

Direct Coombs test and reticulocyte count.

Blood biochemistry: Glucose, blood urea nitrogen, creatinine, lactate dehydrogenase (LDH), uric acid, aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), alkaline phosphatase (ALP), albumin, bilirubin.

Serum protein electrophoresis, serum immunoglobulin levels (preferably),

Viral serological evaluation: All patients should be tested for human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C. In patients with chronically active HBV, antiviral therapy can be initiated before immunosuppressive therapy is administered to reduce the risk of reactivation of hepatitis B. Serology testing for cytomegalovirus (IgM and IgG) should be performed in patients treated with reactivation-related agents (e.g., idelalisib, alemtuzumab).

Performance evaluation

Evaluation of electrocardiography and cardiac functions (left ventricular ejection fraction, rhythm disturbance),

Bone marrow biopsy and aspiration are not recommended at the time of diagnosis. Bone marrow biopsy can be considered in the diagnosis of immune-mediated or disease-related cytopenias.

t(11;14); t(11q;v); +12; del(11q); del(13q); It is recommended to examine the TP53, IGVH mutation status with del(17p),

and PCR/Sanger sequencing. Testing for del17p, TP53 mutation, and IGHV mutation status is critical to select appropriate therapy.

PA chest X-ray should be taken to evaluate hilar and mediastinal adenopathy. Computed tomography (CT) of the thorax, abdomen, and pelvis is not required for pre-treatment evaluation. It can be drawn to evaluate for compression complications, such as obstructive jaundice, obstruction of the inferior vena cava or ureters.

Pregnancy testing in women of childbearing age and men and women of childbearing potential should be counseled about the potential impact of treatment on their fertility and options for fertility preservation measures. Contraception is required during treatment.

Treatment Indications

- Hemoglobin <10 g/dL or platelet count <100,000/microL(Rai stage III-IV; Binet stage C). Cytopenias unrelated to CLL should be excluded. In autoimmune anemia or thrombocytopenia, treatment is given for the autoimmune process. When there is no adequate response to the treatment, the treatment for CLL is started.
- Massive (ie, ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
- Massive (ie, ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
- A greater than 50% increase in lymphocyte count in a two-month period or a lymphocyte doubling time (LDT) of less than 6 months.
- Symptomatic or extranodal involvement leading to loss of function (eg, skin, kidney, lung, spine).
- Patients with any or more of the following symptoms:
- Marked weakness and fatigue (ECOG PS ≥2)
- Excessive night sweats persisting for ≥1 month without evidence of infection
- Unintentional weight loss (more than 10% loss) within 6 months
- Fever above 38°C lasting longer than ≥2 weeks without evidence of infection
- Absolute lymphocyte count alone is not an indication of treatment. Patients with mildly stable and asymptomatic cytopenias (neutrophil<1.000/mm3, Hb<10 gr/dL, platelet<100.000/mm3) can be followed closely without treatment.

Treatment Approach in Early Stage Asymptomatic (Without Active Disease) CLL

For all patients with early-stage asymptomatic CLL (e.g., RAI grade <3, Binet grade A or B), regardless of risk factors (e.g. 17p deletion, unmutated IGHV), the standard of care is a wait-and-see approach rather than immediate treatment. Follow-up with hemogram and clinical examination every three months is recommended. If the disease is stable at the end of the 12-month follow-up, the follow-up period is extended to six months, and treatment is started for patients with an aggressive course and treatment indication.

Some patients with early-stage CLL need treatment within the first few years, while others remain asymptomatic for decades without treatment. Although variable, the median life expectancy in asymptomatic early stage CLL patients is more than 10 years.

Rarely, patients are present with a single enlarged lymph node (Localized SLL). In such a case, instead of recommending systemic chemotherapy or radiotherapy (RT) as in asymptomatic CLL, it is recommended to follow up until symptoms occur. Some experts recommend curative RT, such as early-stage Hodgkin's lymphoma (HL) and follicular lymphoma (FL). However, data on this condition are limited to small retrospective series.[26]

Treatment Approach in Advanced Symptomatic (With Active Disease) CLL

There is no single agreed standard pretreatment regimen for all patients with symptomatic or advanced CLL. There are several initial treatment options. The goals of treatment are to improve symptoms, progression-free survival, and prolong overall survival. While overall survival rates are similar in different regimens, they differ in rates of complete remission, time to progression, and treatment-related toxicities. A choice among these treatments is made according to the characteristics of the patient, the characteristics of the disease and the goals of the treatment.

Treatment-free median survival in patients with advanced CLL (symptomatic or progressive) ranges from 18 months to 3 years. With current treatment regimens alone, the expected overall survival can vary from several years to decades, depending on disease characteristics, patient characteristics, and treatment choice.

Treatment Selection

The choice of initial therapy for patients with symptomatic or advanced CLL is based on patient and tumor characteristics, patient preference, and goals of therapy. Currently, there is no single agreed standard treatment for CLL.

Treatment usually includes the following agents administered in combinations:

- Bruton tyrosine kinase (BTK) inhibitors (eg, acalabrutinib, zanubrutinib, ibrutinib)
- BCL2 inhibitor (venetoclax)
- Monoclonal antibodies (eg, rituximab, ofatumumab, obinutuzumab)
- Purine analogs (e.g., fludarabine, pentostatin)
- Alkylating agents (eg, chlorambucil, cyclophosphamide, bendamustine)
- Phosphoinositol-3-kinase enzyme (PI3K) (e.g., idelalisib, zandelisib, duvelisib)

Chemoimmunotherapy

There is no standard pretreatment regimen for patients with symptomatic CLL. A wide variety of combination chemotherapy regimens are used, often combining nucleoside analogues (e.g., fludarabine), alkylating agents (e.g., cyclophosphamide) and biological agents (e.g.,rituximab). The choice of treatment will depend on the person's age, risk of disease, and symptoms. Younger patients who receive FCR have longer progression-free survival than those who receive bendamustine and rituximab (BR). However, this is not the case in patients over 65 years of age, and BR is the preferred option for those who are not suitable for ibrutinib in this age group. The anti-CD20 monoclonal antibody obinutuzumab has been approved for a variety of indications in CLL.

Bruton Tyrosine Kinase Inhibitors

Ibrutinib is an oral covalent inhibitor that binds to BTK and inhibits its kinase activity, leading to apoptosis of CLL cells. Approved for use in patients with CLL with/without prior treatment. Ibrutinib is used as primary

therapy in patients with chromosome 17p13.1 deletions or TP53 mutations for whom immunochemotherapy is not appropriate. Ibrutinib can also be given in combination with BR or obinutuzumab or rituximab.[27,28] Acalabrutinib is a more selective BTK inhibitor than ibrutinib and has demonstrated a good safety and efficacy profile in patients with relapsed/refractory CLL. Acalabrutinib monotherapy can be given alone or in combination with obinutuzumab to previously treated/untreated symptomatic CLL patients.[29]

Phosphoinositol-3-kinase Enzyme (PI3K)

Idelalisib is a potent selective PI3K inhibitor that induces CLL cell death without affecting T and NK cells. It is approved for use in relapsed CLL in combination with rituximab and can be given to patients with poor prognostic factors.

BCL-2 Inhibitors

Venetoclax is a highly selective inhibitor of BCL2, a protein essential for the survival of CLL cells. It has demonstrated an overall response rate of 70-80%, including patients with a 17p deletion or TP53 mutation for whom venetoclax can be given as monotherapy. Venetoclax can also be given in combination with ibrutinib, obinutuzumab or rituximab. Studies have shown that the first-line oral combination of venetoclax and ibrutinib provides complete remission after 12 cycles.[30]

OTHER TREATMENTS

Chimeric antigen receptor T cells (CAR-T Cell)

CAR-T cells are a genetically engineered T cell that targets an antigen (such as CD 19) found on the surface of CLL. It was developed and tested in clinical trials for patients with previously treated CLL.

Hematopoietic Stem Cell Transplant

The role of hematopoietic stem cell transplantation in the treatment of CLL patients is decreasing after new effective agents for relapsed/refractory patients and high-risk patients. Although autologous stem cell transplantation has no place in CLL, allogeneic stem cell transplantation offers a curative approach in patients with CLL, but the timing and execution of stem cell transplantation is still debated given the availability of numerous new agents.

Splenectomy

It may be an option to cure refractory ITP and AIHA where medical therapy has failed.

Radiotherapy

It is an effective treatment method in local symptomatic LAP and isolated Richter transformation.

Leukapheresis

It can be applied in patients with CLL if there are signs and symptoms of hyperviscosity secondary to hyperleukocytosis.

CONCLUSION

Consequently, CLL, is a hematologic malignancy characterized by the uncontrolled proliferation of mature B lymphocytes. Its presentation can range from asymptomatic with the incidental finding of absolute lymphocytosis on a routine blood test, to symptomatic disease requiring immediate intervention. Prognosis of the disease is defined by the presence or absence of specific mutations such as TP53, chromosomal abnormalities such as del(17p), a type of IGHV mutational status, and elevation of B2M and LDH. Treatment of CLL has evolved over the recent years thanks to the development of targeted therapies. The standard of care has shifted from traditional chemoimmunotherapy approaches to targeted therapies including Bruton tyrosine kinase inhibitors (BTKis) and BCL2 inhibitors, administered either as monotherapy or in combination with CD20 monoclonal antibodies. Clinical trials have also recently evaluated combinations of BTKi and venetoclax and showed the combination to be well tolerated and able to induce deep remissions. Development of newer target therapies is ongoing and the therapeutic landscape in CLL is expanding rapidly.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin.* 2023;73(1):17.PMID: 36633525.
2. Hernández JA, Land KJ, McKenna RW. Leukemias, myeloma, and other lymphoreticular neoplasms. *Cancer.* 1995;75(1 Suppl):381.
3. Fitzmaurice C, Allen C, Barber RM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. *JAMA Oncol*, 2017;3(4):524-548.
4. Yamamoto JF, Goodman MT. Patterns of leukemia incidence in the United States by subtype and demographic characteristics, 1997-2002. *Cancer Causes Control.* 2008;19:379.
5. Miranda-Filho A, Piñeros M, Ferlay J, et al. Epidemiological patterns of leukaemia in 184 countries: a population-based study. *Lancet Haematol* 2018;5(1):e14-e24.
6. Yang S, Varghese AM, Sood N, et al. Ethnic and geographic diversity of chronic lymphocytic leukaemia. *Leukemia.* 2021;35(2):433-439.
7. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood.* 2018;21;131(25):2745-2760.
8. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. *Blood.* 1975;46(2):219-234.
9. Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer.* 1981;48(1):198-206.
10. Lazarian G, Munger M, Quinquenel A, et al. Clinical and biological characteristics of leukemia cutis in chronic lymphocytic leukemia: A study of the French innovative leukemia organization (FILO). *Am J Hematol.* 2021;96(9):E353-E356.
11. Strati P, Uhm JH, Kaufmann TJ, et al. Prevalence and characteristics of central nervous system involvement by chronic lymphocytic leukemia. *Haematologica.* 2016;101(4):458-465.
12. Poitou-Verkinder AL, Francois A, Drieux F, et al. The spectrum of kidney pathology in B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma: a 25-year multicenter experience. *PLoS One* 2015;10(3):e0119156.
13. Baer MR, Stein RS, Dessypris EN. Chronic lymphocytic leukemia with hyperleukocytosis. The hyperviscosity syndrome. *Cancer.* 1985;56(12):2865-2869.

14. Diehl LF, Ketchum LH. Auto immune disease and chronic lymphocytic leukemia: auto immune hemolytic anemia, püre red cell aplasia, and auto immune thrombocytopenia. *Semin Oncol.* 1998;25(1):80-97.
15. Parikh SA, Leis JF, Chaffee KG, et al. Hypogammaglobulinemia in newly diagnosed chronic lymphocytic leukemia: natural history, clinical correlates, and outcomes. *Cancer.* 2015;121(17):2883-2891.
16. Nowakowski GS, Hoyer JD, Shanafelt TD, et al. Using smudge cells on routine blood smears to predict clinical outcome in chronic lymphocytic leukemia: a universally-available prognostic test. *Mayo Clin Proc.* 2007;82(4):449-453.
17. Rawstron AC, Villamor N, Ritgen M, et al. International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia. *Leukemia.* 2007;21(5):956-964.
18. Ben-Ezra J, Burke JS, Swartz WG, et al. Small lymphocytic lymphoma: a clinicopathologic analysis of 268 cases. *Blood.* 1989;73(2):579-587.
19. Thomas R, Ribeiro I, Shepherd P, et al. Spontaneous clinical regression in chronic lymphocytic leukaemia. *Br J Haematol.* 2002;116(2):341-345.
20. Pflug N, Bahlo J, Shanafelt TD, et al. Development of a comprehensive prognostic index for patients with chronic lymphocytic leukemia. *Blood.* 2014;124(1):49-62.
21. Moreno C, Hodgson K, Ferrer G, et al. Auto immune cytopenia in chronic lymphocytic leukemia: prevalence, clinical associations, and prognostic significance. *Blood.* 2010;116(23):4771-4776.
22. Zenz T, Vollmer D, Trbusek M, et al. European Research Initiative on CLL (ERIC). TP53 mutation profile in chronic lymphocytic leukemia: evidence for a disease specific profile from a comprehensive analysis of 268 mutations. *Leukemia.* 2010;24(12):2072-2079.
23. International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol.* 2016;17(6):779-790. .
24. Montserrat E, Vinolas N, Reverter JC, et al. Chronic lymphocytic leukemia in early stage "smoldering" and "active" forms in chronic lymphocytic leukemia. In: Scientific Advances and Clinical Developments, Cheston BD (Ed), Marcel Decker, New York 1993. p.281.
25. Chemotherapeutic options in chronic lymphocytic leukemia: a meta-analysis of the randomized trials. CLL Trialists' Collaborative Group. *J Nat Cancer Inst.* 1999;91(10):861-868.
26. Morrison WH, Hoppe RT, Weiss LM, et al. Small lymphocytic lymphoma. *J Clin Oncol.* 1989;7(5):598-606.
27. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2019;20(1):43-56.
28. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib–rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med*. 2019;381:432-43.
29. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment naïve chronic lymphocytic leukemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet.* 2020;395(10232):1278-1291.
30. Weirda WG et al. Ibrutinib (Ibr) plus venetoclax (Ven) for first-linetreatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): 1-year disease-free survival (DFS) results fromthe MRD cohort of the Phase 2 CAPTIVATE study. American Society of Hematology Annual Meeting 2020: oral presentation.