Chronic Lymphocytic Leukemia: An Overview of Diagnosis, Prognosis, and Treatment

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) is a form of non-Hodgkin lymphoma (NHL) and the most common adult leukemia in Western countries.\(^1,3\) CLL and small lymphocytic lymphoma (SLL) are similar in that they each affect lymphocytes and the primary cancers can be located in bone marrow and lymphoid tissue.\(^4,5\) A key difference is that the primary cancer can also be found in the blood in CLL, whereas in SLL the disease can also be found in the lymph nodes.\(^5\)

In the United States, the incidence rate of CLL is 4.7 new cases per 100,000 people per year. An estimated 20,940 cases will be diagnosed in 2018, with approximately 4510 deaths resulting from the disease.\(^6\) The average lifetime risk of CLL is about 1 in 175, and men have a 1.5 to 2 times greater risk of developing CLL compared with women.\(^3,7,8\) The incidence of CLL increases with age; CLL is rarely observed in people under age 40 years. The median age at diagnosis is between 67 and 72 years.\(^2,3,7\)

Family history of hematologic malignancy (eg, leukemia, NHL, and CLL) is the greatest risk factor for CLL.\(^9,10\) The risk of CLL in those with first-degree relatives with CLL is 8.5 times greater than in patients with no family history.\(^9\) Individuals in families of Eastern origin (eg, China, Korea, and Japan) have a low incidence of CLL independent of the current country of residence.\(^7\) Lifestyle and occupational factors may also play a role in CLL risk. High rates of CLL have been identified in people who live or work on farms or work as hairdressers.\(^10\) Lymphoproliferative disorders, including CLL, have been linked to hepatitis C infections.\(^7,10\)

Although a single CLL-specific genomic aberration has not been identified, ≥80% of CLL cases do exhibit chromosomal abnormalities.\(^7\) Four common genomic alterations exist and include aberrations on chromosomes 11, 12, 13, and 17. Gene studies have identified more than 20 susceptibility loci for B-cell biology and apoptotic pathways.\(^7\)

Median overall survival has been estimated to be 10 years, but survival durations vary from months to decades.\(^7\) Patients with CLL have a shorter life expectancy than age- and sex-matched populations.\(^11,12\)

Pathophysiology and Presentation

CLL is a lymphoproliferative disorder characterized by the clonal proliferation and progressive accumulation of morphologically mature, monomorphic B lymphocytes in the blood, bone marrow, and lymphatic tissues.\(^4,5,7,12,13\) The diagnosis of CLL is based on the following criteria: peripheral monoclonal B-lymphocyte counts ≥5 x 10⁹/L; characteristic cell immunophenotype; coexpression of CD5, CD23, and Kappa; and weak expression of CD20, CD79b, and surface immunoglobulin. CLL cells may also express CD19 and CD200.\(^7\) SLL represents a different expression of the same disease as CLL and is diagnosed based on the presence of lymphadenopathy, splenomegaly, and ≤5 x 10⁹/L abnormal B lymphocytes circulating in the peripheral blood.\(^2,4,5,7\)

The presentation of CLL is diverse. Many patients have no symptoms at diagnosis, require no or delayed initial treatment, and have a good prognosis; however, some patients present with palpable lymphadenopathies,
spleenomegaly, and early, aggressive disease.\textsuperscript{5} CLL is usually recognized when blood counts performed for unrelated reasons reveal lymphocytosis. B symptoms are rarely present. Patients with advanced CLL may exhibit fatigue and intolerance to physical exercise because of anemia that is secondary to bone marrow infiltration. The incidence of bleeding events secondary to low platelet count is very rare.\textsuperscript{7}

**Staging and Prognostic Indicators**

Staging is performed to define disease burden, predict median survival, and indicate prognosis. The most common staging systems for CLL are the Rai and Binet systems.\textsuperscript{4,5,14,15} The Rai system, more commonly used in the United States, differentiates among 3 risk groups based on blood and bone marrow counts and physical examinations; stages range from 0 (low-risk status) to III to IV (high-risk status). The Binet system, widely used in Europe, categorizes groups into 3 stages (A-C) based on the number of lymphoid sites, hemoglobin values, and platelet values.\textsuperscript{4,5,14-16} The Lugano Modification of Ann Arbor staging system is used for SLL and bases staging I to IV on the extent of nodal and extranodal disease status.\textsuperscript{5,17}

DNA sequencing, cytogenetics (eg, fluorescence in situ hybridization and flow cytometry), and evaluation for serum markers are useful in assessing the prognosis of patients.\textsuperscript{5} IGHV mutational status is a significant predictor of outcome; patients with unmutated IGHV have a poor prognosis that is independent of the stage of disease.\textsuperscript{5} IGHV mutation status is preferred over flow cytometry; however, if IGHV status is not available, flow cytometry for CD38, ζ-chain–associated protein kinase 70 (ZAP-70), and CD49d may be useful surrogate markers. Currently, testing for CD38, ZAP-70, and CD49d is not standardized or reproducible across laboratories, and it is not recommended outside clinical trials. Mutations in the BTK gene and phospholipase Cy2 genes may also be unfavorable, especially during therapy with ibrutinib (a Bruton tyrosine kinase [BTK] inhibitor). NOTCH1, SF3B1, and BIRC3 gene mutations may demonstrate variable prognostic significance.\textsuperscript{5}

CLL heterogeneity can exist within the same patient over time. Genomic alterations can occur over the course of the disease and are influenced by treatments; the alterations ultimately affect the disease prognosis.\textsuperscript{7}

Compared with age- and gender-matched cohorts, patients with CLL have a higher risk of developing other cancers. It is unknown whether the increased risk is due to chemoimmunotherapy or immunological defects. The risk of a second cancer is 2.38 times higher in patients treated with fludarabine, cyclophosphamide, and rituximab (FCR) than in the general population. In general, these patients tend to have a poor prognosis.\textsuperscript{18}

**Treatment**

*When to Initiate Treatment*

The clinical course of CLL is extremely varied. Approximately one-third of patients with CLL never require treatment and die from causes other than CLL. Other patients may develop disease-related signs and symptoms that require treatment at varying times after their diagnosis.\textsuperscript{7} The decision to initiate treatment for CLL is based on the presence of progressive disease. The signs and symptoms of progressive disease are detailed in **TABLE 1**.\textsuperscript{4,7}

Patients with early-stage or low-risk (Lugano stage II-IV for SLL; Rai 0 or Binet A for CLL) and intermediate-risk (Rai I-II, Binet B) disease can be monitored without treatment until advanced disease is present. Advanced-stage/high-risk disease (Rai III-IV, Binet C) with progressive cytopenia requires treatment.\textsuperscript{4,5} In patients with localized SLL (Lugano stage I), locoregional radiation therapy is indicated in most patients except those with certain comorbidities or with the potential for long-term toxicity.\textsuperscript{3}

**TABLE 1. Signs and Symptoms of Progressive CLL**\textsuperscript{4,7}

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>Progressive bone marrow failure</td>
<td>Occurrence or worsening of anemia; thrombocytopenia due to bone marrow infiltration</td>
</tr>
<tr>
<td>Bulky disease</td>
<td>Massive (&gt;10 cm) or rapidly progressive lymphadenopathies; massive (&gt;6 cm below left coastal margin) or rapidly progressive splenomegaly</td>
</tr>
<tr>
<td>Uncontrolled autoimmune cytopenias</td>
<td>Autoimmune anemia and/or thrombocytopenia not responsive to steroid treatment</td>
</tr>
<tr>
<td>Rapid lymphocyte doubling time*</td>
<td>&lt;6 months; &gt;50% increase in ≤2 months</td>
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<tr>
<td>Presence of B symptoms</td>
<td>Fever &gt;38°C for ≥2 weeks without infection; unintentional weight loss ≥10% in the previous 6 months; night sweats without infection for &gt;1 month; significant fatigue (not able to perform usual activities)</td>
</tr>
</tbody>
</table>

\*In patients with <30 x 10\textsuperscript{9} lymphocytes/L, the lymphocyte doubling time should not be used as a single parameter to define disease progression requiring treatment.

\textsuperscript{CLL indicates chronic lymphocytic leukemia.}
**Treatment Response**

Complete and partial remissions are considered beneficial responses to treatment, whereas stable disease and progressive disease are considered treatment failures. Strict criteria for responses based on the surrogate markers of tumor burden were revised by the International Workshop on CLL in 2008. In general, complete remission is the disappearance of the disease on a clinical level, including bone marrow evaluation. Partial remission is a $\geq 50\%$ reduction of disease, stable disease is change of $-49\%$ to $49\%$, and progressive disease is a $\geq 50\%$ increase. Refractory disease is characterized by treatment failure or disease progression within 6 months of treatment. Relapse occurs if the disease progresses after 6 months of a beneficial treatment response.4

Because the development of new therapies has affected the predictability of previous definitions of treatment response on outcomes, response criteria have been evaluated to better predict outcomes.5,19 Tumor flare reactions with lenalidomide (ie, painful enlargement of lymph nodes, lymphocytosis, splenomegaly, fever, rash, and bone pain) may meet criteria for progressive disease, according to the 2008 criteria; however, tumor flare may be predictive of a clinical response from lenalidomide.5,19,20 Additionally, ibrutinib, acalabrutinib, idelalisib, and duvelisib may yield a transient or prolonged lymphocytosis that is not indicative of treatment failure.5 A new response category of partial response with lymphocytosis represents patients with a reduction in lymph nodes, splenomegaly, and other markers of beneficial response and no signs of progressive disease other than lymphocytosis.19

**Treatment Selection**

Decisions regarding the treatment of patients with CLL are based on several factors, including patient status, genetic profile, disease status, and response to previous treatments (TABLE 2).7

The first-line standard-of-care treatment for CLL is FCR. It yields a high overall response rate of up to 95%, with a 70% complete response rate; however, this regimen is preferred only in select patients.21 Some patients have remained in remission for at least a decade after FCR treatment, especially those with mutated IGHV.22 Research is focused on toxicity minimization and shortening the duration of treatment to reduce overall exposure to the chemoimmunotherapy.7 Of note, fludarabine is not a treatment option for TP53 and del(17p) mutations due to refractoriness to therapy; patients with these mutations have a poor prognosis and are likely to experience treatment resistance and relapse.5,7

Over time, patients have the potential to relapse or become refractory to treatment. Patients who experience remission duration of at least 2 to 3 years should receive the same chemoimmunotherapy regimen as their previous course, although caution is advised for cumulative toxicities (eg, bone marrow toxicity with FCR). Patients who are refractory or relapse within 2 to 3 years should not be treated with the same regimen and should consider clinical trial enrollment.7

**Novel Therapies**

Several novel therapies with specific cancer cell targets are indicated for use in CLL. They have demonstrated improved outcomes for patients and are briefly discussed herein. Overall, the novel therapies offer the advantage of oral treatment, as well as different and more specific drug targets.

**BTK Inhibitors**

Ibrutinib is an inhibitor of BTK, a signaling molecule of the B-cell receptor (BCR) and cytokine receptor pathway that is involved in B-cell trafficking, chemotaxis, and adhesion. It inhibits malignant B-cell proliferation and survival.
Ibrutinib is indicated for the treatment of CLL and SLL with or without del(17p) and is taken as an oral capsule or tablet once daily.\textsuperscript{23}

Acalabrutinib is a second-generation BTK inhibitor and is effective in patients with relapsed or refractory CLL. It is administered as an oral capsule twice a day.\textsuperscript{5,24} Acalabrutinib should not be used in patients with BTK C481S mutations who are refractory to ibrutinib.\textsuperscript{5}

**B-Cell Lymphoma 2 Inhibitor**

Venetoclax is a selective, small molecule inhibitor of B-cell lymphoma 2 (BCL-2), an antiapoptotic protein that may be overexpressed in CLL cells. It allows for the apoptosis of tumor cells that overexpress BCL-2. Venetoclax is indicated as a once-daily oral dose for the treatment of CLL and SLL with or without del(17p) in patients who have received at least 1 prior therapy.\textsuperscript{25}

**PI3K Inhibitors**

Idelalisib is an inhibitor of phosphoinositide 3-kinase (PI3K), which is included in several B-cell signaling pathways (including BCR, CXCR4, and CXCR5) involved in the trafficking and homing of B cells to the lymph nodes and bone marrow. It inhibits and reduces chemotaxis, adhesion, and cell viability. Idelalisib is indicated for relapsed CLL in combination with rituximab in patients in whom rituximab alone would not be considered appropriate therapy due to comorbidities. It is also recommended for patients who have received at least 2 prior systemic therapies. Idelalisib is taken orally, twice daily.\textsuperscript{26}

Duvelisib is a dual inhibitor of PI3K-δ and PI3K-γ isoforms in different B-cell signaling pathways (BCR and CXCR12-mediated chemotaxis of malignant B cells) and has demonstrated the induction of growth inhibition and reduction of viability of malignant B cells and primary CLL tumor cells. Duvelisib is indicated for relapsed/refractory CLL/SLL after 2 prior therapies as a twice-daily oral dose.\textsuperscript{27}

**Hematopoietic Cell Transplantation**

The role of hematopoietic cell transplantation (HCT) is changing with the emergence of novel pharmacologic treatments. Allogeneic HCT has been shown to provide long-term benefits for patients with del(17p) and TP53 mutations. With the availability of small molecule inhibitors (eg, ibrutinib and venetoclax) that have favorable outcomes in patients with del(17p) and TP53 mutations who are refractory to or have relapsed on first-line therapies, allogeneic HCT may be reserved for patients who have first used small molecule inhibitors.\textsuperscript{5}

**Conclusions**

Investigators continue research to identify reliable, reproducible, and readily accessible prognostic factors to aid in treatment decisions and improve the overall course of CLL. Many patients undergoing therapy will eventually relapse or progress, resulting in the need for multiple lines of therapy and novel therapeutic options. Because there is no standard of care for CLL, many challenges and questions exist. Research is needed to determine the best treatment regimen for patients who are contemplating the diversity of genetic mutations and factors when initiating treatment.

The potential development of further mutations and the changing factors that can occur during the course of the disease must be considered when treatment decisions are made. As response rates and durations increase and the understanding of CLL of improves, patients may face longer treatment durations, greater exposure to therapies, and longer contact with the toxicities associated with therapies. Research is needed to optimize treatment strategies to limit toxicities and increase overall quality of life. As patients continue to live for many years with CLL, additional treatment options are needed—those that will simplify regimens with fewer adverse effects and toxicities and those that will target aggressive, relapsed, or refractory disease. Continued research to find a pharmacologic cure, as well as to learn more about cause and prevention, is needed as well.

**REFERENCES**

THE EMERGING ROLE OF TARGETED THERAPIES FOR THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA


