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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 10^9/L; characteristic cell immunophenotype; coexpressing CD5, CD23, and K/λ; 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 10^9/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,

splenomegaly, and early, aggressive disease.[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.[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.[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.[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.[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.[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.[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 Cγ2 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.[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.[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.[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.[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**.[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.[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.[5]

TABLE 1. Signs and Symptoms of Progressive CLL[4,7]

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

CLL indicates chronic lymphocytic leukemia.
[a]In patients with <30 x 10^9 lymphocytes/L, the lymphocyte doubling time should not be used as a single parameter to define disease progression requiring treatment.

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 ≥50% reduction of disease, stable disease is change of –49% to 49%, and progressive disease is a ≥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]

TABLE 2. Factors Affecting Treatment Decisions in CLL[7]

Category	Factors
Patient status	Age
	Comorbidity burden
	Performance status
	Functional status
	Renal function
	Mental status
	Need for a caregiver
Genetic profile	*TP53* mutation
	del(17p) mutation
	IGHV mutation
	Other mutations
Disease status and treatment response	First treatment
	Secondary treatment
	Relapse
	Refractoriness to last treatment
	Intolerance to treatment
	Adverse reactions
	Toxicities

CLL indicates chronic lymphocytic leukemia.

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.[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.[5,24] Acalabrutinib should not be used in patients with *BTK* C481S mutations who are refractory to ibrutinib.[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.[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.[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.[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.[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

1. Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Blood.* 1997;89(11):3909-3918.
2. Hallek M. Chronic lymphocytic leukemia: 2017 update on diagnosis, risk stratification, and treatment. *Am J Hematol.* 2017;92(9):946-965. doi: 10.1002/ajh.24826.
3. About chronic lymphocytic leukemia. American Cancer Society website. cancer.org/content/dam/CRC/PDF/Public/8679.00.pdf. Updated May 10, 2018. Accessed July 18, 2018.
4. Hallek M, Cheson BD, Catovsky D, et al; International Workshop on Chronic Lymphocytic Leukemia. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. *Blood.* 2008;111(12):5446-5456. doi: 10.1182/blood-2007-06-093906.
5. NCCN Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 2.2019. National Comprehensive Cancer Network website. nccn.org/professionals/physician_gls/pdf/cll.pdf. Updated October 5, 2018. Accessed October 18, 2018.
6. Cancer stat facts: Leukemia – chronic lymphocytic leukemia. NIH/National Cancer Institute/Surveillance, Epidemiology, and End Results Program website. seer.cancer.gov/statfacts/html/clyl.html. Accessed November 7, 2018.
7. Scarfò L, Ferreri AJ, Ghia P. Chronic lymphocytic leukaemia. *Crit Rev Oncol Hematol.* 2016;104:169-182. doi: 10.1016/j.critrevonc.2016.06.003.
8. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018;68(1):7-30. doi: 10.3322/caac.21442.
9. Goldin LR, Björkholm M, Kristinsson SY, Turesson I, Landgren O. Elevated risk of chronic lymphocytic leukemia and other indolent non-Hodgkin's lymphomas among relatives of patients with chronic lymphocytic leukemia. *Haematologica.*

2009;94(5):647-653. doi: 10.3324/haematol.2008.003632.

10. Slager SL, Benavente Y, Blair A, et al. Medical history, lifestyle, family history, and occupational risk factors for chronic lymphocytic leukemia/small lymphocytic lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr*. 2014;2014(48):41-51. doi: 10.1093/jncimonographs/lgu001.
11. Shanafelt TD, Rabe KG, Kay NE, et al. Age at diagnosis and the utility of prognostic testing in patients with chronic lymphocytic leukemia. *Cancer*. 2010;116(20):4777-4787. doi: 10.1002/cncr.25292.
12. Strati P, Shanafelt TD. Monoclonal B-cell lymphocytosis and early-stage chronic lymphocytic leukemia: diagnosis, natural history, and risk stratification. *Blood*. 2015;126(4):454-462. doi: 10.1182/blood-2015-02-585059.
13. Chronic lymphocytic leukemia treatment (PDQ)–health professional version. NIH/National Cancer Institute website. cancer.gov/types/leukemia/hp/cll-treatment-pdq. Updated February 7, 2018. Accessed July 18, 2018.
14. 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.
15. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. *Blood*. 1975;46(2):219-234.
16. Eichhorst B, Robak T, Montserrat E, et al; ESMO Guidelines Committee. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(suppl 5):v78-v84. doi: 10.1093/annonc/mdv303.
17. Cheson BD, Fisher RI, Barrington SF, et al; Alliance, Australasian Leukaemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell Lymphoma Consortium; Italian Lymphoma Foundation; European Organisation for Research; Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Médula Ósea; German High-Grade Lymphoma Study Group; German Hodgkin's Study Group; Japanese Lymphoma Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068. doi: 10.1200/JCO.2013.54.8800.
18. Benjamini O, Jain P, Trinh L, et al. Second cancers in patients with chronic lymphocytic leukemia who received frontline fludarabine, cyclophosphamide and rituximab therapy: distribution and clinical outcomes. *Leuk Lymphoma*. 2015;56(6):1643-1650. doi: 10.3109/10428194.2014.957203.
19. Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. *J Clin Oncol*. 2012;30(23):2820-2822. doi: 10.1200/JCO.2012.43.3748.
20. Chanan-Khan A, Miller KC, Lawrence D, et al. Tumor flare reaction associated with lenalidomide treatment in patients with chronic lymphocytic leukemia predicts clinical response. *Cancer*. 2011;117(10):2127-2135. doi: 10.1002/cncr.25748.
21. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2005;23(18):4079-4088. doi: 10.1200/JCO.2005.12.051.
22. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. *Blood*. 2016;127(3):303-309. doi: 10.1182/blood-2015-09-667675.
23. Imbruvica [prescribing information]. Sunnyvale, CA: Pharmacyclics LLC; 2018. imbruvica.com/docs/librariesprovider7/default-document-library/prescribing-information.pdf. Accessed November 7, 2018.
24. Calquence [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017. accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf. Accessed November 7, 2018.
25. Venclexta [prescribing information]. North Chicago, IL: AbbVie Inc; 2018. accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf. Accessed November 7, 2018.
26. Zydelig [prescribing information]. Foster City, CA: Gilead Sciences Inc; 2018. gilead.com/~/media/CF1E73FFB80B42E2A39F9F5758DB3001.ashx. Accessed November 7, 2018.
27. Copiktra [prescribing information]. Needham, MA: Verastem Inc; 2018. accessdata.fda.gov/drugsatfda_docs/label/2018/211155s000lbl.pdf. Accessed November 7, 2018.