42 - 112 Chronic Lymphocytic Leukemia

112 Chronic Lymphocytic Leukemia

least eight or more cycles. This leads to a significant increase in MRD negativity and improved survival. Anti-CD22 Monoclonal antibodies directed against CD22 are linked to cytotoxic agents, such as calicheamicin (inotuzumab ozo gamicin), or to plant or bacterial toxins (epratuzumab). In a random ized trial of relapsed or refractory ALL patients, the CR rate was 66% and significantly superior to the CR rate with standard chemo therapy. Inotuzumab is now included in first-line therapy for Ph+ and Ph– patients. Anti-CD19 Targeting CD19 is of great interest because this antigen is highly expressed in all B-lineage cells, most likely including early lymphoid precursor cells. A new promising approach is the bispecific antibody blinatumomab, which combines single-chain antibodies to CD19 and CD3, such that T cells lyse the CD19-bearing B cells. Blinatumomab is particularly effective in MRD-positive patients, with a 70–80% conversion to MRD negativity, translating into improved overall survival; ~25% of MRD-negative patients survived without any further treatment. Blinatumomab has also moved to frontline therapy. CAR-T Cells The adoptive transfer of CAR-modified T cells directed against CD19 is a promising approach for the treatment of CD19+ childhood or adult ALL. In the first three larger studies in adults with relapsed or refractory ALL, the CR rate ranged from 67 to 91% with MRD negativity in 60–81% of the patients who achieved CR. Overall survival is 50% or more at ≥2 years, which is remarkable for these heavily pretreated patients. CAR-T cells are also effective in CNS leukemia and in other extramedullary sites. CAR-T cell therapy in relapsed or refrac tory ALL was first considered as a bridge to allogeneic SCT, applied in 10–50% of patients, but the necessity for an allogeneic SCT after CAR-T cells is unclear. CAR-T cell therapies are also moving to the frontline. CD19-negative relapses after CAR-T cell therapy or blinatumomab due to downregulation of CD19 expression are a relevant obstacle. Toxicities of Immunotherapies The anti-CD22 agent inotu zumab ozogamicin is associated with hepatotoxicity, including venoocclusive disease, particularly after allogeneic SCT, but can be managed by reduced dosing and limitation of cycles. For anti-CD19 therapies, cytokine release syndrome and severe neurotoxicity are the most prominent toxicities and often require intensive care unit care (more so after CAR-T cells than blinatumomab). Management of these compli cations has improved with early recognition. Because toxic death after immunotherapies is very low compared to intensive chemotherapy or allogeneic SCT, immunotherapies are now increasingly included in frontline therapy. ■ ■TREATMENT OF T-ALL Immunotherapy for T-ALL is still not available, and intensive chemo therapy is still the mainstay in combination with the T cell–specific drug nelarabine. Currently, γ-secretase targeting NOTCH1, checkpoint inhibitors such as bortezomib and venetoclax, and HDAC inhibitors are being explored. ■ ■CONCLUSION AND

FUTURE DIRECTIONS Cytogenetic and molecular analysis at diagnosis allows identification of ALL subentities requiring different treatment options. Evaluation of MRD is the most important parameter for treatment decisions. The greatest progress has been achieved by targeted therapies, such as TKIs for Ph+ ALL and new immunotherapeutic approaches. This will lead to further improved outcome of adult ALL patients, 50% of whom are already surviving 5–10 years and are most likely cured. New options and advances, such as low-intensity chemotherapy, reduction of SCT, incorporation of targeted therapies, and reduction of toxicities, will improve the quality of life of patients and lead to individualized approaches for each patient. ■ ■FURTHER READING Caracciolo D et al: The emerging scenario of immunotherapy for T-cell acute lymphoblastic leukemia: Advances, challenges and future perspectives. Exp Hematol Oncol 12:5, 2023.

Gökbuget N et al: Diagnosis, prognostic factors and assessment of

ALL in adults: 2023 ELN recommendations from a European expert panel. Blood 143:1891, 2024. Gökbuget N et al: Management of ALL in adults: 2023 ELN recom mendations from a European expert panel. Blood 143:1903, 2024. Hoelzer D et al: ESMO Clinical Practice Guideline interim update on the use of targeted therapy in acute lymphoblastic leukaemia. Ann Oncol 35:15, 2024. Prockop S, Wachter F: The current landscape: Allogeneic hemato poietic stem cell transplant for acute lymphoblastic leukemia. Best Pract Res Clin Haematol 36:101485, 2023. Ribera J-M, Chiaretti S: Modern management options for Ph+ ALL. Cancers 14:4554, 2022. Shimony S et al: Nelarabine: when and how to use in the treatment of T-cell acute lymphoblastic leukemia. Blood Adv 8:23, 2024. Short N et al: Using immunotherapy and novel trial designs to optimise front-line therapy in adult acute lymphoblastic leukaemia: Breaking with the traditions of the past. Lancet Haematol 10:e382, 2023. CHAPTER 112 Jennifer A. Woyach, John C. Byrd

Chronic Lymphocytic

Leukemia Chronic Lymphocytic Leukemia Chronic lymphocytic leukemia (CLL) is a monoclonal proliferation of mature B lymphocytes defined by an absolute number of malignant cells in the blood (5 × 109/L). The presence of malignant B cells under this count in the blood without nodal, spleen, or liver involvement and absent cytopenias is a precursor of this disease called monoclonal B-cell lymphocytosis (MBL) with ~1–2% chance per year of progressing to overt CLL. CLL is a heterogeneous disease in terms of natural history, with some patients presenting asymptomatically and never requiring therapy, whereas most will need therapy and a small subset will pres ent with symptomatic disease, require multiple lines of therapy, and eventually die of their disease. Over the past two decades, the under standing of CLL origin and biology has grown exponentially, leading first to more refined disease definition, prognostic markers, and, subse quently, introduction of novel therapies that have significantly changed the natural history of this disease to where only a small minority will die from CLL. In this way, CLL has served as a prototype of a cancer where understanding the biologic underpinnings in absence of unified mutation drivers has informed therapy development. In this chapter, we review the epidemiology, biology, and management of CLL, with a focus on new knowledge that has changed and continues to change standards of care. EPIDEMIOLOGY CLL is primarily a disease of older adults, with a median age at diag nosis of 71 and an age-adjusted incidence of 4.6/100,000 people in the United States; 18,740 peoples were diagnosed and 4490 people died of CLL in the United States in 2023. The prevalence

of CLL has increased over the past decades due to improvements in therapy for this disease and also survival of older patients from other medical ailments. In 1980, the 5-year overall survival of patients was 70%, and this increased to 92% in 2015 and is likely even higher today. The male-to-female ratio is 2:1; however, as patients age, the ratio becomes more even, and over the age of 80, the incidence is equal between men and women. The disease is most common in Caucasians, less common in Hispanic and African Americans, and is rare in the Asian population. Unlike many other malignancies, there have been no definitive links between CLL and exposures. Indeed, CLL is one of the only types of

leukemia not linked to radiation exposure. Agent Orange exposure has been implicated, and CLL is thus a service-connected condition for those who were exposed to Agent Orange in the Vietnam conflict, burn pit exposure from the Middle East conflicts, and Camp Lejune water.

CLL is one of the most familial-associated malignancies, and the first-degree relative of a CLL patient has an 8.5-fold elevated risk of developing CLL than the general population. MBL is also more com mon in families with two first-degree relatives having CLL, further sup porting a genetic predisposition of this disease. Despite this, specific genes conferring risk in the familial setting outside of specific families have been difficult to identify. In genome-wide association studies (GWAS), ~30 single nucleotide polymorphisms (SNPs) have been identified, which is estimated to account for 19% of the familial risk of CLL. Genes involved in apoptosis, telomere function, B-cell receptor (BCR) activation, and B-cell differentiation have all been implicated in GWAS. Variants in shelterin complex proteins involved in telomere maintenance such as POT1 have been identified in a small number of families. BIOLOGY AND PATHOPHYSIOLOGY ■ ■CELL OF ORIGIN The cell of origin in CLL has not definitively been established. The morphology, immunophenotype, and gene expression pattern of CLL cells are that of a mature B cell (Fig. 112-1), and so it has long been presumed that the initiating cell is a mature lymphocyte, perhaps memory B cells. However, many facets of CLL biology do not support this idea, including antigen-binding characteristics of CLL cells and the presence of stereotyped BCRs. Other possibilities include a stepwise process including a series of transforming events at various stages of B-cell development, potentially including de-differentiation of more mature cells. The self-renewing, multipotent hematopoietic stem cell (HSC) might also be the originating cell of CLL, postulated based on transplant studies in mice showing clonal leukemic cell development with different characteristics from donor leukemia after transplanta tion of HSC from CLL patients. More work will be required to elucidate the origins of CLL. PART 4 Oncology and Hematology ■ ■B-CELL RECEPTOR SIGNALING IN CLL Perhaps the most important advancement in CLL biology is the under standing of the role of BCR signaling in the disease. CLL has distinct BCR signaling as compared to normal B cells, which is characterized by low-level IgM expression, variable response to antigen stimulation, and tonic activation of antiapoptotic signaling pathways that promote tumor survival. CLL cells by gene expression profiling share many features with antigen-activated mature B cells, suggesting a role for activation of BCR signaling in the disease pathogenesis. Tissue-based microarrays have revealed upregulation of BCR pathway genes in the lymph nodes and bone marrow compared to the peripheral blood, FIGURE 112-1 Chronic lymphoid leukemia in the peripheral blood. (From Williams Hematology, 7th ed, in M Lichtman et al [eds]: New York, McGraw-Hill, 2005.)

suggesting a particular importance of this pathway in microenviron mental homing. Fitting with the role of BCR signaling in CLL, one of the most influ ential prognostic factors identified in this disease

is the mutational status of the immunoglobulin heavy chain variable (IGHV) region. During normal B-cell maturation, the variable regions of the immu noglobulin heavy chain undergo somatic hypermutation. In CLL, ~60% of patients have IGHV that is ≥2% mutated from germline. This may indicate a more mature, postgerminal center progenitor, and is typically associated with a more indolent disease course. Conversely, ~40% of patients will have IGHV <2% mutated from germline, which is associated with more rapid progression of disease and short survival before the era of therapeutics that target BCR. Unfavorable biologic properties including enhanced telomerase activity, overexpression of activation-induced cytidine deaminase, increased nuclear factor-κB (NF-κB) activity, high-risk genomic mutations (e.g., NOTCH1, SF3B1, TP53, ATM), and clonal evolution are also associated with IGHV unmutated disease. In addition to the mutational status of IGHV, about 30% of CLL patients express “stereotyped” BCRs, where the stereotype subset predicts clinical course, with subsets 1 and 2 predicting higherrisk disease. ■ ■CYTOGENETIC ABNORMALITIES Besides IGHV mutational status, recurrent cytogenetic abnormalities are the most robust prognostic factor clinically available in CLL. These abnormalities are typically identified by fluorescent in situ hybridiza tion (FISH) analysis; however, stimulated metaphase karyotype has a role as well. The most well-characterized abnormalities include del(13) (q14.3), trisomy 12, del(11)(q22.3), and del(17)(p13.1) (Fig. 112-2). The presence of sole del(13)(q14.3) is associated with more indolent disease, prolonged survival, and good response to traditional therapies. Usually this abnormality is not seen on banded karyotype analysis, and when present on karyotype, it indicates a larger deletion involving the retinoblastoma gene, which negates the favorable prognosis associated with this marker. Trisomy 12 has a more intermediate prognosis. The del(11)(q23.3) results in deletion of the ATM gene and is associated with bulky lymphadenopathy and aggressive disease in young patients, with inferior prognosis, and more rapid progression to symptomatic disease. The del(17)(p13.1) results in loss of one allele of the tumor suppressor TP53 and is associated with the poorest prognosis in CLL with rapid disease progression, poor response to traditional thera pies, and shorter survival. Other abnormalities have been shown to be important in smaller studies but are not routinely performed at all centers. Finally, complex karyotype (three or more abnormalities) on stimulated metaphase karyotype analysis has significant adverse impact on time to treatment and overall survival, with data indicating that increasing complexity is even more deleterious to response and survival. Clonal evolution, or acquisition of cytogenetic or molecular abnor malities, is common in CLL, especially in patients with IGHV unmu tated CLL. Because the cytogenetics of patients can change even in the absence of therapy, it is recommended that FISH, with or without cytogenetics, is checked before every line of therapy, mostly to evaluate acquisition of del(17)(p13.1). ■ ■GENE MUTATIONS AND MIR ALTERATIONS Compared with many other malignancies, the genome in CLL is rela tively simple, with an average CLL genome carrying ~20 nonsynony mous alterations and ~5 structural abnormalities. And, unlike many other hematologic malignancies, there is no unifying genetic lesion, and most recurrent genetic driving mutations exist at frequencies of <5%. Whole genome and whole exome sequencing have identified the most common mutations in CLL to be in SF3B1, NOTCH1, MYD88, ATM, and TP53 (Table 112-1). Most of the identified mutations in these genes are common among different malignancies, and with the exception of MYD88, they are generally identified with much higher frequency in IGHV unmutated disease. NOTCH1 mutations are present in ~15% of CLL patients and are commonly associated with trisomy 12. Although multiple different

Patients surviving (%)

108 120 132 144 156 168 Months No. at Risk

17p deletion 11q deletion 12q trisomy Normal 13q deletion as sole abnormality FIGURE 112-2 Outcomes among CLL patients with various cytogenetic abnormalities. (From The New England Journal of Medicine, Genomic Aberrations and Survival in Chronic Lymphocytic Leukemia, H Dohner et al: 343: 1910. Copyright @2000 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.) mutations are seen, most are located within the PEST (proline, glu tamic acid, serine, and threonine) domain and result in constitutive NOTCH signaling. NOTCH1 mutations have been associated with lower sensitivity to CD20 antibody therapy and increased risk of transformation to aggressive diffuse large B-cell lymphoma (DLBCL; Richter's transformation), although its relevance in the era of targeted therapies is less clear. SF3B1 is a component of the RNA spliceosome and is mutated in 10–15% of CLL cases. Mutations appear to be associ ated with intermediate-risk disease, and functionally, SF3B1 may be important in the response to DNA damage. Mutations of the tumor suppressor TP53 are found in ~5% of CLLs in previously untreated early-stage disease and up to 40% in later stages. TABLE 112-1 Recurrent Mutations in CLL GENE FREQUENCY OF MUTATIONS (%) SF3B1 8–14 TP53 5–13 NOTCH1 10–13 MYD88 4–8 ATM 8–11 BIRC3 <5 XPO1 <5 FBXW7 <5 POT1 <5 BRAF <5 EGR2 <5 IKZF3 <5 Abbreviation: CLL, chronic lymphocytic leukemia.

17p deletion 11q deletion 12q trisomy Normal 13q deletion as sole abnormality CHAPTER 112

Seventy percent of the time, these mutations coexist with del(17)(p13.1), effectively eliminating TP53 function. As expected, and consistent with other malignancies, TP53 mutations are associated with a poor prognosis and expected lack of response to DNA-damaging therapies. ATM mutations, which are heterogeneous and occur throughout the gene, occur in 10–15% of CLL patients. ATM mutations often coexist with del(11)(q22.3), eliminating ATM on the alternate allele. Similar to TP53, mutations in ATM tend to result in impaired response to DNA damage, which can reduce responsiveness to chemotherapy. In contrast to the aforementioned mutations, those in MYD88 tend to occur in IGHV-mutated CLL and be associated with a more indolent prognosis. This gene is involved in Toll-like receptor signaling, and the most common mutation, L265P, results in constitutive activation and NF-κB activity. Along with abnormalities in coding genes, it has become appar ent that noncoding genes such as microRNAs are recurrently altered in CLL. The most common cytogenetic abnormality, del(13)(q14.3), results in loss of the miR15/16 cluster, which is important in the patho genesis of CLL. In normal cells, miR15A/miR16A inhibits antiapop totic gene expression (including BCL2, CCND1, CCND3, and CDK6), and this specific deletion allows for overexpression of these genes and thus increased cell survival. Loss of other miR expression such as miR181a leads to overexpression of proteins such as the antiapoptotic genes MCL1 and TCL1. Overexpression of miR-155, an onco-miR associated with B-cell transformation, has also been documented in the majority of CLL patients. ■ ■IMMUNOLOGY CLL is characterized by dysregulation of the normal immune system in addition to the malignant immune cells. Besides numerical abnormali ties due to bone marrow dysfunction, even in the early stages of disease, there are skewed ratios of immune cells and functional abnormalities.

Innate immune system defects associated with CLL include reduced complement proteins and activity, qualitative neutrophil defects, and functional defects of natural killer cells.

More focus has been placed on the impairments in the adaptive immune system in this disease. Within the CD4+ T-cell compartment, a qualitative defect is noted similar to chronic antigen stimulation inducing a phenotype of T-cell exhaustion typical of what is seen in chronic viral infections such as hepatitis. This has been demonstrated to lead to impaired T-cell cytotoxic capacity and reduced proliferative ability. Additionally, there are physical changes in the T-cell cytoskel eton that cause impaired immune synapse formation with antigen presenting cells. In addition to a lack of capacity to respond to patho gens, the T-cell defect in CLL also likely leads to tumor cell tolerance. During the course of the disease, the polarization of the CD4+ T cells shifts from a Th1 (cytotoxic) phenotype to a Th2 phenotype, which leads to expansion of immunosuppressive cytokines such as interleukin (IL) 10. Additionally, in the later stage of disease, T regulatory cells are expanded, which contributes to an immunosuppressive phenotype. Other components of the immune microenvironment are altered as well to form a more supportive environment for the malignant cells. M2 monocytes have been shown to differentiate into a type of tumorassociated macrophage known as a nurse-like cell in CLL. These cells promote survival by secreting chemokines and cytokines that increase migration and activation. PART 4 Oncology and Hematology The humoral immune system in CLL is also dysregulated, as is expected for a malignancy that results in very few normal B cells. Hypogammaglobulinemia is very common and affects all subclasses of immunoglobulins, occurring in ~85% of patients at some time in their disease course, and is more common as disease progresses. A correla tion between low IgG and IgA and infection risk has been established, but isolated IgM reduction does not seem to be associated with excess infection risk. Also, CLL cells can secrete monoclonal IgM or IgG in a small number of cases, and this can correlate with disease progression. CLINICAL PRESENTATION AND DIAGNOSIS OF CLL ■ ■CLINICAL PRESENTATION AND DIAGNOSIS The presentation of CLL most commonly occurs as an incidental diagnosis made at the time of medical evaluation for another cause. In this regard, CLL is most commonly diagnosed on routine blood work demonstrating an elevated lymphocyte count in asymptomatic indi viduals, although some patients present with symptoms and require early therapy. When noting either an elevated total white blood cell (WBC) count with lymphocytic predominance or a normal WBC with a differential showing a lymphocytosis, the next step is to perform flow cytometry on the peripheral blood. In CLL, this will reveal the typical immunophenotype that includes the typical B-cell markers CD19, CD20, CD22, CD23, CD200, the T-cell marker CD5 (CD5 is also expressed on the B1 subset of B cells that typically has unmutated immunoglobulin and responds to antigens independent of cognate T-cell help), and dim surface immunoglobulin of either kappa or lambda type (Table 112-2). Atypical phenotypes can be seen as well and usually can be differentiated on the basis of morphology, cytoge netics, or clinical presentation. In cases in which the clonal B-cell count based on flow cytometry is ≥5 × 109/L, no further workup is needed to confirm the diagnosis of CLL. Some patients will present with a small clonal proliferation of CLL cells in the peripheral blood but will also have lymphadenopathy or TABLE 112-2 Typical Immunophenotype of CLL Compared with Other B-Cell Malignancies DISEASE CD5 CD10 CD19 CD20 CD23 CYCLIN D1 SURFACE IG CLL + − +

- (dim)
-

−

- (dim) Mantle cell lymphoma
-

− +

- (mod/bright) −
- (mod/bright) Marginal zone lymphoma −/+ −
- (mod/bright) −/+ −
- (mod/bright) Follicular lymphoma −
-

− Abbreviation: CLL, chronic lymphocytic leukemia.

splenomegaly. In these cases, the likely diagnosis is small lymphocytic lymphoma (SLL), a semantic designation from CLL that denotes a pri marily tissue-based disease rather than bone marrow/blood-based dis ease. The genetic and molecular features of SLL are identical to those of CLL. The retention of the cells in tissues may be related to the expres sion of a particular adhesion molecule. Thus, SLL patients are managed identically to CLL patients, and often in the later stages of disease, these patients will have blood and bone marrow involvement as well. MONOCLONAL B-CELL LYMPHOCYTOSIS Patients who do not meet the diagnostic criteria for CLL based on quantification of clonal B cells in the peripheral blood and who do not have associated signs of CLL including lymphadenopathy, organo megaly, or cytopenias have a disorder known as monoclonal B-cell lymphocytosis (MBL), which is now thought to precede every case of CLL. Analogous to monoclonal gammopathy of uncertain significance (MGUS) in myeloma, not all MBL progresses to CLL. MBL is initially characterized by a CLL-like immunophenotype in ~75% of cases but can also be atypical (CD23 negative or bright CD20) or CD5 negative. More relevant for prognosis is characterization by count, with lowcount MBL defining patients with <0.5 × 109 clonal B cells/L and highcount MBL defining patients with >0.5 × 109 but <5 × 109/L. Patients with low-count MBL have a negligible rate of progression to CLL, whereas those with high count progress to overt CLL at a rate of 1–2% per year, warranting continued monitoring. Population-based stud ies have estimated the prevalence of MBL up to ~12% in the general population, where it is most common in elderly men. It is especially common in first-degree relatives of CLL patients, where the frequency is ~18%. Although the risk of MBL progression is relatively low, it has become apparent that patients still experience complications that sug gest an immune dysfunction in MBL that is similar to that seen with CLL. Rates of serious infections requiring hospitalization appear to be significantly increased in MBL, similar to the rates seen in CLL. In a case-control study, patients with MBL had a 16% chance of hospitaliza tion over a 4-year time period, compared with 18.4% in patients with newly diagnosed CLL. Secondary cancers also appear to be increased in MBL. These data suggest that monitoring for patients with MBL should focus on vaccinations and age-appropriate cancer screening, as the probability of complications appears to be higher than the risk of progression in most of these patients. Follow-up for patients with MBL can occur with the primary care physician as this does not represent a malignancy, whereas CLL is mostly co-managed with both a primary care physician and a hematologist. COMPLICATIONS OF CLL A significant amount of morbidity and mortality related to CLL is due to complications of the disease. In general, complications besides dis ease progression include infections, secondary cancers, autoimmune complications, and transformation to a more aggressive clonally related lymphoma. ■ ■INFECTIONS Infections are a leading cause of both disease-related morbidity and death in patients with CLL, with ~30–50% of deaths in CLL patient attributed to infection. Owing to the

immune dysfunction associ ated with the disease, patients are at risk for both typical and atypical infections. Besides this baseline risk of infections, most CLL therapies, even targeted therapies, can increase infection risk. Viral prophylaxis

is also indicated for many patients when therapy is initiated (even with targeted agents) and for patients with a history of varicella-zoster to diminish reactivation and morbidity from this virus. Because of the abnormalities in cellular and humoral immunity, vaccine responses in CLL are limited in many patients, especially in the later stages of disease. In one study, one dose of 13-valent pneu mococcal vaccine produced an adequate immune response in only 58% of patients compared with 100% in age-matched controls. Vaccine efficacy can be improved in CLL patients by repeated booster vaccina tions, vaccine adjuvants, and protein conjugation. Despite the known limitations, vaccination against influenza, COVID-19, varicella-zoster, pneumococcal pneumonia (Prevnar 20), and respiratory syncytial virus is recommended in CLL. The recombinant zoster vaccine has approximately a 60% response in previously untreated CLL, is safe, and should be considered for this patient group. Efficacy of the newer 20-valent pneumococcal vaccine in patients with CLL has not yet been reported. In contrast, live vaccines should be avoided in the setting of CLL because of the small risk of viral reactivation with an immuno compromised host. Vaccine effectiveness in terms of humoral response is also decreased by most CLL therapies, although this can be overcome in some cases by booster vaccinations. When possible, receiving vaccinations before the initiation of therapy is recommended. As discussed earlier, hypogammaglobulinemia is common in CLL and can be associated with significant risk for infections, primarily of mucocutaneous etiology such as sinusitis and bronchitis. In addition, women can have frequent urinary tract infections. While administra tion of prophylactic intravenous immunoglobulin (IVIg) has not been shown to improve survival, it has been shown to reduce the number of minor or moderate bacterial infections, and thus is indicated in patients with hypogammaglobulinemia who suffer from recurrent infections or have pulmonary bronchiectasis. It is also our practice to administer at least one dose of immunoglobulin to CLL patients who develop influenza with coexisting hypogammaglobulinemia to diminish risk of postinfluenza pneumococcal pneumonia. IVIg is also indicated in patients who have been hospitalized for a serious infection and in those whose IgG level is <300–500 mg/dL. ■ ■SECONDARY MALIGNANCIES Multiple population-based studies have shown that patients with CLL are at an elevated risk of developing other cancers, with a rate up to three times that of the general population, even in the absence of cytotoxic chemotherapy. The most common types of cancers seen in CLL are skin, prostate, and breast cancers, although other cancers are seen as well. Skin cancers are particularly common, with a rate of 8- to 15-fold higher than the general population, and may behave more aggressively. All CLL patients should be counseled on the use of sunscreen while outdoors and should undergo preventative skin examinations at least yearly. In one single-center study, older age at CLL diagnosis, male sex, high β2-microglobulin, high lactate dehydrogenase (LDH), and chronic kidney disease were associated with excess risk of other cancers; other CLL-specific risk factors have not shown association with other cancer risk. While cancer risk is higher, there are no specific recommendations for increased cancer screening in CLL patients. Age- and sex-appro priate screenings should be recommended. In addition, we extend screening beyond age 70–75 years for CLL patients based on the higher frequency of cancers. Conflicting data exist regarding the risk of cancers after CLL-specific therapy. Chemoimmunotherapy, in particular alkylator-containing regimens, seems to be associated with an increased risk for second ary cancers. Secondary cancers are also seen in the setting of targeted therapies. Bruton tyrosine kinase (BTK) inhibitors

appear to have a secondary cancer risk similar to what is seen in the CLL population in general, but potentially a higher rate of nonmelanoma skin cancers. Compared with chemoimmunotherapy, venetoclax plus obinutuzumab has been associated with a numerically but not statistically higher rate of secondary cancers at follow-up of 6 years.

■ ■AUTOIMMUNE COMPLICATIONS Autoimmune complications are frequent in CLL. Most commonly, these include autoimmune cytopenias, but autoimmune complications of other organs including glomerulonephritis, vasculitis, and neu ropathies have also been reported. Of the autoimmune cytopenias, the most common is autoimmune hemolytic anemia (AIHA), which is an antibody-mediated destruction of autologous red blood cells (RBCs). Second most common is immune thrombocytopenia (ITP), which shares some features with AIHA and has a similar mechanism targeting platelets. These two syndromes may occur in isolation, sequentially in the same patient, or present in combination as Evan's syndrome. Pure red cell aplasia (PRCA) and autoimmune granulocytopenia (AIG) are comparatively rare and can occur alone or in combination with other autoimmune cytopenias. It is difficult to tease out whether autoim mune cytopenias lead to worse prognosis in CLL because of various complicating factors. However, it is clear that these can lead to sig nificant morbidity, both due to the process itself and due to therapies required for management.

AIHA usually presents as an isolated anemia with an elevated reticu locyte count and features of hemolysis including elevated bilirubin and LDH and low haptoglobin. Detection of a warm IgG antibody on the surface of RBCs with a Coombs test can help solidify the diagnosis, although Coombs-negative cases can occur. Immediate therapy is almost always necessary and consists of transfusion and immunosup pression. Glucocorticoids are often used for initial therapy, although in most cases, additional treatment is needed due to either poor response or recurrence with taper of steroid dosing. Rituximab can be success ful, and therapy directed toward the underlying CLL is often effective in more resistant cases. Transfusion of blood in cases of robust AIHA must be initiated with caution as transfusion reactions can be seen due to poorly matched blood, but it should be pursued in those with severe, symptomatic anemia. Death from uncontrolled AIHA can occur in the absence of appropriate supportive care. ITP can be more difficult to diagnose, as it may be difficult to dif ferentiate from progression of disease due to the lack of laboratory tests that identify platelet destruction from this mechanism. Signs that point toward ITP include isolated thrombocytopenia and rapid decline in platelet levels in the absence of an alternative etiology. A bone mar row biopsy showing normal or increased megakaryocytes can be used to confirm the diagnosis but is often not necessary. In CLL, treatment for ITP is usually instituted when platelet levels drop to 20,000–30,000 or if there is evidence of bleeding complications or need for invasive procedures. Like AIHA, initial therapy consists of glucocorticoids and IVIg, with rituximab also being an effective method to induce longterm remissions. Also, the thrombopoietin receptor agonists romip lostim and eltrombopag are effective in secondary ITP. In many cases, ITP can be successfully treated without treating the underlying CLL. In cases in which anemia or thrombocytopenia appear, it is impor tant to investigate the mechanism because the approach to therapy of autoimmune cytopenias in CLL differs from that for cytopenias due to marrow replacement. ■ ■RICHTER'S TRANSFORMATION One of the most devastating complications of CLL is Richter's trans formation, transformation of CLL to an aggressive lymphoma, most commonly DLBCL. The World Health Organization also recognizes Hodgkin's lymphoma (HL) as a variant of Richter's transforma tion; other aggressive lymphomas

are rarely identified. Some older series have included prolymphocytic transformation in this category, although this has much less prognostic impact on long-term outcome. The prevalence of Richter's transformation is difficult to estimate based on previous studies, but one prospective observational study estimated a rate of 0.5% per year for DLBCL and 0.05% per year for HL. Risk factors for development include bulky lymphadenopathy, NOTCH1 mutations, del(17)(p13.1), and a specific stereotyped IGVH usage. Lymphomas arising in the setting of CLL can either be clonally related or unrelated to the initial CLL, with prognosis significantly better for clonally unrelated lymphomas. In addition, patients with Hodgkin's transformation have improved outcome when treated with standard

Hodgkin's disease treatment. B-cell prolymphocytic leukemia (PLL) arising from CLL is currently classified as Richter's transformation as well; however, clinical features and therapy are quite different, so these two should be differentiated for therapeutic purposes.

Clinical signs of Richter's transformation include rapid progression in adenopathy, often in a specific area, and constitutional symptoms including fatigue, night sweats, fever, and weight loss. LDH is usually high. In suspected cases, the first step is 18FDG-PET/CT (fluorode oxyglucose–positron emission tomography combined with computed tomography) scan to localize an area for biopsy. Standardized uptake values (SUVs) <5 are consistent with CLL and can rule out Richter's transformation in many cases. SUVs >5 are suspicious for Richter's transformation, with SUVs ≥10 being very concerning. Excisional biopsy is the preferred mode of diagnosis, and fine-needle aspiration should be discouraged. Therapy for DLBCL Richter's transformation usually involves com bination chemoimmunotherapy. Outcomes are poor, with median survivals of 6–16 months in most series for clonally related Richter's versus ~5 years for clonally unrelated. This highlights an area of unmet need in CLL therapy and an area of active investigation. Intensive chemotherapy is ineffective for most patients and results in significant toxicity. For fit patients who achieve a response with therapy, stem cell transplantation has the possibility to induce long-term remissions and should be explored. In addition, chimeric antigen receptor (CAR) T-cell (CAR-T) therapy has shown promising results in small groups of patients and remains an area of active clinical investigation. Limited data using bispecific antibodies are also encouraging. Patients with Hodgkin's disease can be treated according to the algorithm for this disease, with many individuals being cured. PART 4 Oncology and Hematology WORKUP OF CLL AND APPROACH TO THERAPY ■ ■WORKUP AND STAGING Workup of a patient with new diagnosis of CLL based on typical immunophenotyping includes a detailed history of infectious disease; family history of CLL; and careful physical examination with attention to the lymph nodes, spleen, and liver. In patients desiring to know the expected natural history of their CLL, prognostic testing using FISH and stimulated karyotype and sequencing for TP53 and IGHV muta tion status can be performed. Imaging with CT scan is usually not necessary unless there are symptoms and concern for intraabdominal nodes out of proportion to peripheral nodes. Bone marrow biopsy is not undertaken until therapy is initiated, except in cases of unexplained cytopenias. ■ ■STAGING There are two widely used staging systems in CLL: The Rai staging system is used more commonly in the United States, whereas the Binet system is more commonly used in Europe. Both characterize CLL on the basis of disease bulk and marrow failure (Table 112-3). Both rely on physical examination and laboratory studies and do not require TABLE 112-3 Staging of CLL Rai Staging System Low risk (stage 0) Lymphocytosis only Intermediate risk (stage I/II) Lymphocytosis with lymphadenopathy, with or without splenomegaly or hepatomegaly High risk (stage III/IV) Lymphocytosis with anemia

or thrombocytopenia due to bone marrow involvement Binet Staging System A <3 areas of lymphadenopathy B ≥3 areas of lymphadenopathy C Hemoglobin ≤10 g/dL and/or platelets <100,000/μL Abbreviation: CLL, chronic lymphocytic leukemia.

TABLE 112-4 CLL International Prognostic Index Risk Score VARIABLE ADVERSE FACTOR RISK SCORE TP53 status Deleted or mutated

IGHV mutational status Unmutated

> 3.5 mg/L

β2-Microglobulin concentration Clinical stage Rai I–IV or Binet B–C

Age

> 65 years

Implications of Risk Score 5-YEAR SURVIVAL (TRAINING SET DATA) RISK SCORE RISK CLASSIFICATION 0-1 Low 93.2% 2-3 Intermediate 79.3% 4-6 High 63.3% 7-10 Very high 23.3% imaging or bone marrow analysis. While the initial staging systems could reliably predict survival in CLL, with the changes in therapy since the original description of the stages, the impact of initial stage on survival is not as clear. Cytogenetic and genomic testing can help refine outcome of these staging tests. An international collaboration integrated both clinical and genomic staging to better predict outcome at diagnosis and time of initial treatment, which led to development of the CLL International Prognostic Index (Table 112-4). This index has been shown to be useful in prediction of both time to first treatment and outcome with chemoimmunotherapy. Validation in the setting of novel targeted therapies has not occurred. ■ ■CRITERIA FOR THE INITIATION OF THERAPY Currently, a watchful waiting strategy is used for most patients with CLL, with therapy reserved for patients with symptomatic disease. This recommendation is based on multiple trials showing no survival advantage with earlier therapy, although this question continues to be a focus of active investigation. With the exception of patients participating in early intervention studies in CLL, disease-related symptoms that require the initiation of therapy are outlined in Table 112-5. Except for the rare patient who presents with disease requiring urgent therapy, in most cases, these symptoms can be monitored over short periods to determine related ness to CLL and need for therapy. ■ ■INITIAL THERAPY FOR CLL Over the past decade, the initial therapy of CLL has dramatically changed. Whereas chemoimmunotherapy was once standard for all patients, now most patients are treated with oral therapies targeted TABLE 112-5 Criteria for the Initiation of Therapy Symptoms Indicating Need for Therapy in CLL Evidence of progressive marrow failure (worsening of anemia or thrombocytopenia not due to autoimmune destruction) Massive (≥6 cm below costal margin), progressive, or symptomatic splenomegaly Massive (≥10 cm), progressive, or symptomatic lymphadenopathy Progressive lymphocytosis with an increase of ≥50% over a 2-month period or lymphocyte doubling time <6 months Autoimmune anemia or thrombocytopenia

not responsive to standard therapy Symptomatic or functional extranodal involvement Constitutional symptoms (one or more of the following: unintentional weight loss ≥10% over 6 months, significant fatigue, fevers ≥100.5°F for 2+ weeks without infection, night sweats for >1 month without infection) Abbreviation: CLL, chronic lymphocytic leukemia.

against BTK or BCL2 with an anti-CD20 monoclonal antibody. This continues to be an area of active investigation, with standards of care shifting rapidly. The major classes of these therapies will be outlined here. BTK Inhibitors BTK is an attractive target in CLL because, unlike other kinases in the BCR pathway, BTK does not have natu ral redundancy and is relatively selective for B cells, so inhibition leads to a predominant B-cell–specific phenotype. The first-in-class covalent BTK inhibitor is ibrutinib, which is relatively selective for BTK but also inhibits a number of structurally similar kinases. As initial therapy, ibrutinib was initially compared with chlorambucil (RESONATE study), and there was an 84% lower risk of progression or death with ibrutinib, with 59% of ibrutinib-treated patients alive and progression-free at 7 years. Subsequent studies have compared ibrutinib alone or with the anti-CD20 antibody rituximab to standard chemoimmunotherapy with fludarabine plus cyclophosphamide plus rituximab (FCR) or bendamustine plus rituximab (BR) and shown superiority of targeted therapy to chemoimmunotherapy. Ibrutinib also has immune modulatory roles to expand and also enhance T-cell function that may improve CAR-T efficacy. Side effects noted to occur with this class of agents include arthralgias/myalgias, rash, diarrhea, dyspepsia, bruising/bleeding (particularly when on antiplatelet/antico agulation therapy or with surgery), hypertension, atrial fibrillation, and ventricular arrhythmias. Two second-generation covalent BTK inhibitors, acalabrutinib and zanubrutinib, were developed to be more specific for BTK than ibruti nib and consequentially show better tolerability. Two trials performed in relapsed/refractory CLL have positioned acalabrutinib and zanubru tinib as preferred BTK inhibitors compared with ibrutinib. Acalabru tinib was compared head-to-head with ibrutinib in previously treated patients with high-risk relapsed CLL in the ELEVATE-RR trial. Acala brutinib was shown to be noninferior to ibrutinib in terms of efficacy and to have lower rates of atrial fibrillation, hypertension, myalgias/ arthralgias, bruising, and skin and nail changes than reported with ibrutinib. Zanubrutinib was compared head-to-head with ibrutinib in the ALPINE trial, which enrolled patients with relapsed CLL without regard to risk status. In this study, zanubrutinib was shown to be supe rior to ibrutinib in terms of overall response rate and progression-free survival (PFS). Zanubrutinib was also associated with lower rates of atrial fibrillation but similar rates of other adverse events. Because acalabrutinib and zanubrutinib are newer, follow-up is shorter than with ibrutinib, but all three covalent BTK inhibitors appear to be similarly active in the frontline setting. Acalabrutinib was studied in the treatment-naïve setting in the ELEVATE-TN trial, where acalabrutinib resulted in a 6-year PFS of 62% and acalabrutinib given with obinutuzumab resulted in a 4-year PFS of 78%. Zanubrutinib was studied in treatment-naïve CLL in the SEQUOIA study, where 2-year PFS was 85.5% for patients treated with zanubrutinib. Importantly, with the follow-up that is available from frontline studies of covalent BTK inhibitors in CLL, traditional prognostic fac tors, including IGHV mutational status and FISH, have less impact on outcome. Indeed, age and performance status were the only variables that predicted survival in the ELEVATE-TN trial. BCL2 Inhibitor Venetoclax is an orally bioavailable, selective allosteric inhibitor of the antiapoptotic protein BCL2, which is upregu lated in CLL. Similar to the BTK inhibitors, phase 3 trials support the frontline use of venetoclax in combination with obinutuzumab (VO) compared with chemoimmunotherapy. The CLL14 study compared VO versus chlorambucil plus obinutuzumab in previously untreated patients with coexisting medical conditions. Unlike BTK inhibitors, which are continuously administered until

disease progression, VO treatment is administered for a fixed duration of 1 year. Median PFS for VO was 76.2 months, compared with 36.4 months for patients treated with chlorambucil plus obinutuzumab. The CLL13/GAIA trial also studied VO, as well as VO plus ibrutinib (IVO) and venetoclax plus rituximab (VR), compared with effective chemoimmunotherapy

regimens (FCR for younger patients and BR for older patients) in fit patients. At 4 years, VO and IVO showed superior PFS compared with chemoimmunotherapy (81.8% and 85.5%, respectively, vs 77.2%), but VR was not superior to chemoimmunotherapy. Side effects associated with venetoclax include tumor lysis syndrome, neutropenia, and nau sea/vomiting/diarrhea. Importantly, genomic risk features including IGHV mutational status and FISH/cytogenetics appear to be more relevant to PFS with fixed-duration VO therapy as compared with indefinite BTK inhibitor therapy.

Targeted Therapy Combinations Due to synergy between BTK and BCL2 inhibition, there has been considerable interest in studies combining agents with these two mechanisms to allow for fixedduration therapies. As described earlier, 1-year fixed-duration IVO was shown to be superior to chemoimmunotherapy in previously untreated fit patients in the CLL13/GAIA study. The GLOW study is a registra tion trial comparing ibrutinib plus venetoclax (IV) to chemoimmuno therapy in previously untreated older or unfit patients. In this trial with 1 year of IV, 42-month PFS was 74.6% for IV compared with 24.8% for chlorambucil plus obinutuzumab. Although this study led to regulatory approval of IV in Europe, it is not approved by the U.S. Food and Drug Administration (FDA). It is not yet clear whether IV or IVO is a more effective therapy than the other fixed-duration standard, VO. Current studies are also using more selective inhibitors of BTK in an attempt to improve efficacy and safety of these combinations. CHAPTER 112 Chemoimmunotherapy For the most part, targeted therapy has supplanted chemoimmunotherapy in CLL. However, long-term follow-up of studies of FCR has demonstrated that a subset of patients treated with this regimen can have durable responses over 20 years, with a likely cure of CLL. This group is composed almost exclusively of patients with mutated IGVH and favorable cytogenetics. However, despite the efficacy of this regimen, short- and long-term toxicities limit its adaptability to many patients with IGHV-mutated disease. Short-term toxicities are mostly related to myelosuppression and include neutropenia and infection. Long-term cytopenias are less com mon, but they do occur. Also, there is about a 3–5% risk of therapyrelated myeloid neoplasm with this regimen that is almost always fatal. In the E1912 study of FCR versus ibrutinib plus rituximab (IR), at follow-up, there was no difference in PFS or overall survival between FCR and IR for patients with mutated IGHV, suggesting that a place for this regimen may remain in clinical practice. In addition, current stud ies are focused on limiting chemotherapy and/or adding novel agents in efforts to achieve cure but limit toxicity. Chronic Lymphocytic Leukemia ■ ■THERAPY OF RELAPSED CLL Currently, the mainstays of treatment for relapsed CLL are the same classes as initial therapy, and the choice of second-line therapy is heav ily dependent on the agent that was used in the frontline setting. The optimal sequencing of targeted agents in CLL has not been established; however, the available data suggest that the sequence of either BTK inhibitor and then BCL2 inhibitor and the reverse are both accept able. In addition, some patients treated initially with venetoclax-based regimens can likely be successfully retreated with venetoclax. In a trial of venetoclax for patients who had relapsed after ibrutinib therapy, overall response rate (ORR) was 65%, with a median PFS of ~2 years, in a very heavily pretreated patient population. Retrospective data of a BTK inhibitor given after venetoclax suggest that this sequence is also effective, with an ORR of 84% and median PFS of 32 months. PI3K inhibitors also have activity in relapsed CLL; however, activity follow ing both BTK and

BCL2 inhibitors is likely minimal. In addition, many new agents are in development in CLL, including novel oral targeted therapies, antibodies, and immune-based treatments. Noncovalent Inhibitors of BTK Despite the activity of covalent BTK inhibitors in CLL, a subset of patients will eventually relapse, and the primary mechanism of acquired resistance to ibrutinib, acalabru tinib, and zanubrutinib is acquisition of a mutation at the binding site of the drug (predominantly BTK C481S). Noncovalent BTK inhibitors

TABLE 112-6 Response Criteria in CLL LYMPHOCYTE COUNT LYMPH NODESa SPLEEN/LIVER SIZEb BONE MARROWc PERIPHERAL BLOOD COUNTS CR <4000/μL None >1.5 cm Not palpable Normocellular, <30% lymphocytes, no B lymphoid nodules PR Decrease ≥50% from baseline Decrease ≥50% from baseline Decrease ≥50% from baseline Stable disease Not meeting CR/ PR/PD criteria Not meeting CR/PR/ PD criteria Not meeting CR/PR/PD criteria PD Increase ≥50% Increase ≥50% Increase ≥50% • Platelet count ≤50% of baseline due to CLL • Hemoglobin decrease >2 g/dL due to CLL aRefers to sum of the products of multiple lymph nodes evaluated by CT scan. bBased on physical examination. cBone marrow only required to confirm CR. Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete response; PD, progressive disease; PR, partial response. have been developed to overcome this resistance mechanism by bind ing both reversibly and to alternative sites on BTK. Pirtobrutinib is the first in class of these agents and is an extremely selective inhibitor of BTK that has achieved accelerated approval by the U.S. FDA for use in patients who have been previously treated with both BTK and BCL2 inhibitors. This is based on the BRUIN study, where an overall response rate of 82.2% and median PFS of 19.6 months were seen in a heavily pretreated high-risk group of patients, with equivalent efficacy noted for patients with C481S mutations in BTK. PART 4 Oncology and Hematology Immune Therapies Immune therapies in CLL are currently focused in the relapsed setting and include allogenic stem cell trans plantation, CAR-T therapy, and bispecific antibodies. Stem cell transplantation is a curative approach to CLL. Because most CLL patients are older and many have significant comorbidities, myeloablative transplants incur extensive morbidity and mortality, making them prohibitive in many individuals. Reduced-intensity conditioning (RIC) allogeneic transplants have been successfully incor porated into the treatment of patients up to ~75 years in age but still have a ≥50% frequency of chronic graft-versus-host disease. This is still considered a standard treatment in CLL but has fallen out of favor with the introduction of well-tolerated novel agents, as well as clinical trials of CAR-T therapy. CD19 CAR-T trials have not been as successful in CLL as they have in other B-cell malignancies, due to the immunosup pression associated with the disease. The most robust data have come with lisocabtagene maraleucel (liso-cel), where in the TRANSCEND CLL 004 trial, the ORR was 43%, with a median PFS of 11.9 months in patients previously treated with BTK inhibitors and venetoclax. Many current trials are focused on optimizing CD19 CAR-T by add ing agents such as BTK inhibitors or PI3K inhibitors or modifying the CAR-T structure, and other studies are testing different targets outside of CD19. This area remains a focus of intense investigation in CLL. ■ ■ASSESSING RESPONSE TO THERAPY AND MINIMAL RESIDUAL DISEASE IN CLL Following the completion of therapy or during therapy for indefinite targeted agents, response is initially assessed using physical exami nation and laboratory studies (Table 112-6). If residual disease is not detected using these methodologies, CT scans are used to assess response. Bone marrow biopsies with flow cytometry are indicated if no disease is detected to confirm CR. It has been established in various malignancies that complete tumor eradication is associated with longer survival. In CLL, if no malignant cells can be detected in the bone marrow down to a level of 1 CLL cell in 104 leukocytes (0.01%), the patient is said to be negative for

minimal residual disease (MRD). Following combination

• Platelet count >100,000/µL • Hemoglobin >11 g/dL • Neutrophils >1500/µL Infiltrate ≤50% of baseline One of the following: • Platelet count >100,000/µL or ≥50% from baseline • Hemoglobin >11 g/dL or ≥50% from baseline • Neutrophils >1500/µL or ≥50% from baseline Not meeting CR/PR/PD criteria Not meeting CR/PR/PD criteria chemoimmunotherapy, eradication of MRD correlates with long-term survival and potentially cure in a subset of patients receiving FCR chemoimmunotherapy. Undetectable MRD in blood or bone mar row is also associated with improvement in PFS in venetoclax-based regimens. However, eradication of MRD has not been shown to be a meaningful endpoint with BTK inhibitors as monotherapy. Higher sensitivity of 1 CLL in 106 leukocytes (0.0001%) can be obtained using next-generation sequencing methods such as ClonoSeq. Treatment of MRD-relapsing CLL is being explored as part of clinical trials. ■ ■CONCLUSION CLL is treated only when it becomes symptomatic. At the time of ther apy, FCR chemoimmunotherapy in a small subset of young patients with very good risk CLL is potentially curative. In the majority of patients with symptomatic CLL, targeted therapy directed at BTK and/or BCL2 can produce durable remissions and allow patients many years of disease-free survival. ■ ■FURTHER READING Brown JR et al: Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med 388:319, 2023. Byrd JC et al: Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: Results of the first randomized phase III trial. J Clin Oncol 39:3441, 2021. Fischer K et al: Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. N Engl J Med 380:2225, 2019. Hallek M et al: iwCLL guidelines for diagnosis, indications for treat ment, response assessment, and supportive management of CLL. Blood 131:2745, 2018. Landau DA et al: Evolution and impact of subclonal mutations in chronic lymphocytic leukemia. Cell 152:714, 2013. Mato AR et al: Pirtobrutinib after a covalent BTK inhibitor in chronic lymphocytic leukemia. N Engl J Med 389:33, 2023. Puente XS et al: Whole-genome sequencing identifies recurrent muta tions in chronic lymphocytic leukaemia. Nature 475:101, 2011. Sharman JP et al: Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naïve chronic lym phocytic leukemia (ELEVATE TN): A randomized, controlled, phase 3 trial. Lancet 395:1278, 2020. Siddiqi T et al: Lisocabtagene maraleucel in chronic lymphocytic leukaemia and small lymphocytic lymphoma (TRANSCEND CLL 004): A multicentre, open-label, single-arm, phase 1–2 study. Lancet 402:641, 2023. Thompson PA et al: Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. Blood 127:303, 2016.

Revision #1
Created 2026-01-06 16:32:00 UTC by Omar Ayman
Updated 2026-01-06 16:32:00 UTC by Omar Ayman