Current Approach to Diagnosis and Management of Chronic Lymphocytic Leukemia

TAIT D. SHANAFELT, MD, AND TIMOTHY G. CALL, MD

The care of patients with chronic lymphocytic leukemia (CLL) has changed dramatically during the past decade. This review summarizes the work-up of lymphocytosis and the current diagnostic criteria and management of CLL. Although clinical staging (Rai and Binet) remains the foundation for determining prognosis, 50% of patients with early-stage disease at diagnosis will experience an aggressive course of disease with early progression and premature death due to CLL. New laboratory techniques (CD38, fluorescence in situ hybridization [FISH]) can identify some patients with early-stage CLL at high risk of rapid disease progression. The array of treatment options has expanded in recent years and now includes monoclonal antibodies used alone or in combination with purine nucleoside analogues and alkylating agents, which have culminated in dramatically improved response rates. Supportive care guidelines now include vaccination strategies, surveillance for secondary malignancies, and aggressive management of infectious complications. An early hematology consultation is recommended for all patients at diagnosis to identify and counsel high-risk patients with early-stage disease who may benefit from more frequent follow-up or early treatment as part of a clinical trial.


The diagnostic algorithm, prognostic tools, supportive care measures, and treatment of chronic lymphocytic leukemia (CLL) are changing rapidly. Before the advent of automated instruments for performing blood cell counts, CLL was typically diagnosed when patients presented with symptoms of lymphadenopathy, cytopenias, or infection. The diagnosis of CLL was based primarily on peripheral blood lymphocyte morphology with limited ability to distinguish CLL from the leukemic phase of other subtypes of non-Hodgkin lymphoma. Clinical staging (Rai or Binet) was the limit of prognostication, and “watchful waiting” was the cornerstone of management. Chronic lymphocytic leukemia was believed to be a disease of elderly persons that was characterized by an indolent course, and most clinicians counseled patients that they would likely die of causes unrelated to CLL before they would require treatment. The infectious complications, increased risk of autoimmune disorders, and increased risk of secondary malignancy associated with CLL were less well defined and clinically underappreciated. The foundation of treatment, monotherapy with alkylating agents, was reserved for patients with advanced-stage disease and was characterized by a low complete response rate.

Nearly all these paradigms have changed. In 2004, CLL is likely to be diagnosed when an elevated lymphocyte count is discovered incidentally during a complete blood cell count (CBC) obtained for an unrelated indication. Immunophenotyping, flow cytometry, and cytogenetic evaluation allow increased diagnostic precision and distinguish CLL from mantle cell lymphoma, hairy cell leukemia, splenic marginal zone lymphoma, and peripheral T-cell malignancies. Recent reports state that 50% of patients with early-stage CLL experience rapidly progressive disease, require therapy, and have a median survival period that is significantly shorter than suggested by the original publications of the Rai and Binet staging systems. Most patients diagnosed as having CLL, including the majority of patients with early-stage disease, die of CLL or CLL-related complications. Novel therapeutic strategies, including monoclonal antibodies, combination chemotherapy, and, for selected patients, stem cell transplantation, have dramatically improved response rates and are likely to lead to improvements in overall survival. New laboratory tests can identify some patients with early-stage CLL at high risk of early disease progression, and clinical trials of treatment of these patients are under way.
Although these advances have increased the importance of early hematology consultation at diagnosis, the burden of diagnosis, supportive care, and appropriate referral is the responsibility of the primary care provider. We summarize the recent advances in diagnosis, prognostic tools, treatment, and supportive care measures relevant to the primary care provider of patients with CLL.

DIAGNOSING CLL—THE MODERN APPROACH TO EVALUATING LYMPHOCYTOSIS
Chronic lymphocytic leukemia, a clonal disorder of mature B cells, is one of the most common lymphoid malignancies in the United States. Chronic lymphocytic leukemia affects more than 100,000 Americans, with an estimated 15,000 new diagnoses per year.8 In the new World Health Organization classification, CLL and small lymphocytic lymphoma are considered a single disease entity (CLL).9 The median age range at diagnosis is 60 to 68 years with a male preponderance (ratio of women to men, approximately 1:1.8).1,3 The clinical manifestations of CLL include fever, night sweats, weight loss (>10% body weight), fatigue, frequent infections, organomegaly (spleen and liver), and cytopenias.1

With the advent of automated instruments for performing blood cell counts, CLL in most patients is diagnosed incidentally when an unexpected elevation of the absolute lymphocyte count (ALC) is discovered on a CBC. The diagnosis of CLL should be considered any time a patient presents with an ALC greater than 5.0 × 10⁹/L without clear etiology. The differential diagnosis of lymphocytosis is broad and includes a number of malignant and reactive conditions. Before making a diagnosis of CLL, reactive causes of lymphocytosis and the leukemic phase of other lymphoproliferative disorders, particularly mantle cell lymphoma, must be excluded. The optimal evaluation and management of individuals with a persistent ALC of 3.0 × 10⁹/L to 5.0 × 10⁹/L are unknown. We perform the same diagnostic evaluation for these patients and approach patients with a CLL phenotype on flow cytometry in the same manner as patients with early-stage CLL (Rai 0).8 The differential diagnosis and recommended work-up for patients with lymphocytosis are presented in Figure 1.

Flow cytometry with immunophenotyping is able to establish the diagnosis of CLL in most patients (Table 1). Once the diagnosis of CLL is confirmed, patients should undergo staging and additional laboratory evaluation to help the physician predict prognosis and guide treatment. The staging work-up includes a physical examination (lymph nodes examination, assessment for enlargement of spleen or liver), sequential CBC (to determine lymphocyte doubling time [LDT]), and examination of the peripheral blood smear. Bone marrow aspirate and biopsy are elective for asymptomatic patients at the time of diagnosis. Bone marrow biopsy is recommended before initiating chemotherapy9 and may provide additional prognostic information.

PROGNOSTIC TOOLS FOR CLL—BEYOND STAGING
Clinical Staging and LDT
The goal of prognostic tools is to enable patients and physicians to predict the natural history of a disease, improve their ability to make treatment decisions, and help patients to plan their lives. For CLL, clinical staging systems were some of the first prognostic tools, and they have been helpful for patient counseling and for grouping individuals with a similar natural history for research purposes.

In 1975, Rai et al10 developed a clinical “staging” criteria for patients with CLL that separates patients into different prognostic groups based on the presence of lymphadenopathy, organomegaly (spleen and liver), and cytopenias. Rai et al showed a correlation between these clinical stages and prognosis10 and later modified the 5-stage system to a 3-stage system that categorizes patients as having low risk (original Rai stage 0), intermediate risk (original Rai stages I-II), or high risk (original Rai stages III-IV) disease.11 The staging criteria and median survival using the Rai staging system are presented in Table 2. Other clinical characteristics, including advanced age, male sex, and comorbid disease, also appear to be associated with worse prognosis.5,10,12-14

Although staging systems are useful clinical tools for grouping patients into low-, intermediate-, and high-risk CLL, there is marked heterogeneity in the clinical progression of disease in patients at similar stage. Approximately 50% of patients with early-stage disease develop more advanced disease1,4,5 and die of CLL or its complications.1 This highlights the limitations of a prognostic system based solely on markers of disease burden rather than disease biology.

The LDT, a clinical measure that addresses the kinetics of cell growth, is calculated by determining the number of cell growth, is calculated by determining the number of

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The LDT, a clinical measure that addresses the kinetics of cell growth, is calculated by determining the number of months the ALC takes to double. Early studies found that patients with CLL with an LDT of less than 12 months had shorter survival.15 Because patients with advanced-stage disease (stages III and IV) typically require treatment, the prognostic utility of LDT is most important for patients with early-stage disease who typically are treated by watchful waiting. In one study, the estimated survival for patients with early-stage disease and an LDT of less than 12 months was 66 months, whereas no patients with an LDT greater than 12 months had died at the time of analysis (median follow-up, 48 months).15 Although other studies have confirmed the prognostic significance of LDT as an independent predictor of disease progression and shorter
survival, it is confounded by other factors that cause fluctuations in the ALC, making treatment decisions based on this marker alone problematic. Elevation of the μ₂-microglobulin level, another readily available laboratory test, also suggests worse survival.

**Novel Biologic and Molecular Markers**

Historically, clinical stage and LDT have been the most accurate and widely used prognostic tools for counseling patients with CLL. Despite their utility for predicting natural history for populations of patients with CLL, their ability to predict which individuals with early-stage disease will develop advanced-stage disease is imprecise. Recent technological advancements have enabled investigators to search a wider array of biologic and molecular markers to identify differences in disease biology that may predict those patients most likely to develop advanced-stage disease and who may benefit from alternative treatment strategies.
**Table 1. Diagnostic Criteria for CLL**

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Typical method of testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ALC, &gt;5.0 × 10^9/L</td>
<td>Automated blood counter</td>
</tr>
<tr>
<td>2. Clonal B-cell proliferation</td>
<td>Exclusively κ or λ light chain use on flow cytometry</td>
</tr>
<tr>
<td></td>
<td>Immunophenotype consistent with CLL</td>
</tr>
<tr>
<td></td>
<td>CD5+, CD19+, CD20+ (dim), CD23+, dim surface immunoglobulin</td>
</tr>
<tr>
<td>3. Rule out leukemic phase of other lymphoproliferative disorder</td>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>(especially mantle cell lymphoma)</td>
<td>Flow cytometry+; CD23 dim or absent, CD5+, bright CD20+</td>
</tr>
<tr>
<td></td>
<td>FISH: t(11:14)‡</td>
</tr>
<tr>
<td></td>
<td>Cyclin D1 testing positive</td>
</tr>
<tr>
<td></td>
<td>Nodal marginal zone lymphoma</td>
</tr>
<tr>
<td></td>
<td>Flow cytometry+; CD5–, bright CD20</td>
</tr>
<tr>
<td></td>
<td>Hairy cell leukemia</td>
</tr>
<tr>
<td></td>
<td>Flow cytometry+; CD5–, bright CD11c/CD22+, CD19+, bright CD20+, CD103+</td>
</tr>
<tr>
<td></td>
<td>TRAP positive</td>
</tr>
<tr>
<td></td>
<td>Lymphoplasmacytic lymphoma (Waldenström macroglobulinemia)</td>
</tr>
<tr>
<td></td>
<td>Flow cytometry+; CD5–, CD19+, CD 20+, SPEP-associated monoclonal protein (&gt;2.5 g/dL)</td>
</tr>
<tr>
<td></td>
<td>FISH: t(14:18)‡</td>
</tr>
</tbody>
</table>

*ALC = absolute lymphocyte count; CLL = chronic lymphocytic leukemia; FISH = fluorescence in situ hybridization; SPEP = serum protein electrophoresis; TRAP = tartrate-resistant acid phosphatase.
†Flow cytometric results must be correlated with careful pathologic assessment of morphologic features.
‡Translocation of indicated chromosomes.

**Chromosomal Analysis by Conventional Cytogenetics and Interphase Fluorescence In Situ Hybridization.**—Chromosomal analysis to identify specific genomic abnormalities has led to breakthroughs in the diagnosis and treatment of several hematologic malignancies, particularly chronic myelogenous leukemia and acute myelogenous leukemia with translocation (15:17). Conventional cytogenetics testing is difficult in CLL because of the small number of dividing leukemic cells. With the development of fluorescence in situ hybridization (FISH), detection of chromosomal abnormalities in nondoning cells became possible, which intensified interest in chromosomal analysis for patients with CLL.

In 2000, German investigators noted the prognostic significance of chromosomal analysis using interphase FISH for patients with CLL. Chromosomal abnormalities were detected in 82% of patients with CLL, with 55% having 13q–, 18% with 11q–, 16% with trisomy 12, 7% with 17p–, and 29% with more than 1 detectable chromosomal abnormality. A hierarchical model constructed after regression analysis identified differences in survival based on the results of FISH testing. The median survival by FISH category after a median follow-up of 70 months is presented in Table 3, which shows a dramatically worse prognosis for individuals with 17p– or 11q– abnormalities. Interphase FISH is a clinically available test for community-based practitioners; we recommend FISH testing for all patients with newly diagnosed CLL.

**Ig V H Gene Mutational Status.**—Until recently, CLL B cells were believed to be derived from the leukemic transformation of “naive” B lymphocytes that had not undergone the somatic mutation of immunoglobulin genes, which occurs when B cells are exposed to antigen in the germinal center of lymph nodes. In the early 1990s, several studies revealed that approximately one half of patients with CLL have somatic mutation of immunoglobulin chains (immunoglobulin variable region of the heavy chain [Ig V H]), suggesting that a substantial proportion of CLL clones arise from postgerminal center “memory” B cells.

In 1999, 2 groups of investigators reported on the prognostic significance of somatic mutation of Ig V H genes in CLL. When patients with early-stage (Binet A) disease were stratified as Ig V H-mutated (>2% difference in nucleotide sequence of Ig V H genes from germline) or nonmutated (<2% difference in nucleotide sequence of Ig V H genes from germline), significant survival differences were observed. The median survival for patients with early-stage disease with nonmutated Ig V H genes was less than 8 years (95 months), whereas patients with early-stage disease with mutated-type clones had a median survival of greater than 24 years (293 months). Although the prognostic significance of Ig V H has been confirmed by numerous investigators, Ig V H testing is a technically difficult assay that is not currently available for routine use in the United States. Extensive efforts have focused on identifying surrogate markers for Ig V H mutational status.
### Table 2. Rai Staging Criteria*

<table>
<thead>
<tr>
<th>Rai stage</th>
<th>ALC &gt; 5.0 × 10^9/L</th>
<th>Enlarged nodes</th>
<th>Enlarged livet/spleen</th>
<th>Hemoglobin &lt;10.5 g/dL</th>
<th>Platelets &lt;100 × 10^9/L</th>
<th>Median survival† (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>150</td>
</tr>
<tr>
<td>I+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>101</td>
</tr>
<tr>
<td>II +/–</td>
<td>+/–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>71</td>
</tr>
<tr>
<td>III +/–</td>
<td>+/–</td>
<td>+/–</td>
<td>+/–</td>
<td>+</td>
<td>–</td>
<td>19</td>
</tr>
<tr>
<td>IV +/–</td>
<td>+/–</td>
<td>+/–</td>
<td>+/–</td>
<td>+/–</td>
<td>+</td>
<td>19</td>
</tr>
</tbody>
</table>

*ALC = absolute lymphocyte count; + = present; – = absent; +/– = may be either present or absent.
†According to original series by Rai et al.¹⁰

### Ig V_H Mutational Status and CD38 Expression.—
CD38 is a cell surface protein detectable on CLL cells by flow cytometric analysis of peripheral blood. One early report²⁶ about the prognostic significance of Ig V_H mutational status described differences in the membrane expression of CD38 on CLL cells and found an association between higher CD38 expression and nonmutated Ig V_H genes. Subsequent reports substantiated the prognostic significance of CD38 expression but did not validate CD38 expression as a surrogate marker for Ig V_H mutational status.²⁹,³⁰ One study reported an 8-year survival of 92% for patients who were CD38 negative but only 50% for patients who were CD38 positive.³¹ The constancy of CD38 expression on CLL B cells is controversial because numerous groups report changes in CD38 status in as many as 10% to 25% of patients with CLL.²⁹,³⁰,³²,³³ On balance, it appears that CD38 expression status correlates with poorer prognosis, but its use in individual patients is limited because of variation with time and difficulty in standardizing measurement. CD38 expression is not a reliable surrogate marker for Ig V_H mutational status.

### Zeta-Associated Protein 70 and Other Prognostic Markers.—There remains intense interest for developing new, clinically feasible prognostic markers for patients with CLL to more accurately identify those with higher risk of disease progression and early mortality. Gene expression profile analysis (GEPA) is one method of identifying candidate markers. GEPA evaluates the expression of thousands of genes simultaneously and provides a more comprehensive molecular view of the cellular events underlying oncogenesis. GEPA has identified a restricted set of genes that may discriminate between mutated and nonmutated clones in patients with CLL.³⁴-³⁶ One such gene is zeta-associated protein 70 (ZAP-70), a tyrosine kinase normally involved with T-cell signaling, which is expressed differentially by patients with nonmutated CLL clones.³⁴,³⁵,³⁷

Subsequent studies using a variety of potentially clinically available techniques to evaluate ZAP-70 expression (immunohistochemistry, immunoblot techniques, flow cytometry) found that ZAP-70 testing correctly predicts mutational status in approximately 78% to 90% of patients.³⁷,³⁹ More importantly, it has similar ability to predict the time to treatment³⁷,³⁹ and overall survival as Ig V_H mutational status.³⁸ In a report of patients with predominantly (89%) early-stage disease, the estimated median survival for patients whose test results were ZAP-70 positive was 90 months, whereas the median survival was not reached by patients whose test results were ZAP-70 negative (median follow-up, 63 months).³⁸

Although ZAP-70 appears to be a promising prognostic marker for patients with CLL, numerous issues must be resolved before widespread clinical use. Larger trials confirming the stability⁴⁰ and independent prognostic significance²⁹,³⁰,³² of this marker are needed, and the optimal method to assess ZAP-70 expression for clinical purposes must be determined. Although beyond the scope of this review, several other markers, including serum thymidine kinase levels,⁴³-⁴⁶ serum β₂-microglobulin,⁴⁷-⁴⁹ serum-soluble CD23,⁵⁰,⁵¹ and markers of angiogenesis,³²,⁵¹ have shown promise and warrant further investigation.

### Table 3. Prognosis by FISH Result for Patients With CLL²²⁸

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Median survival (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17p–</td>
<td>2.5</td>
</tr>
<tr>
<td>11q–</td>
<td>6.6</td>
</tr>
<tr>
<td>12+</td>
<td>9.0</td>
</tr>
<tr>
<td>None</td>
<td>9.0</td>
</tr>
<tr>
<td>13q–</td>
<td>11.0</td>
</tr>
</tbody>
</table>

*CLL = chronic lymphocytic leukemia; FISH = fluorescence in situ hybridization.

### Summary of Prognostic Tools
Although clinical stage remains the foundation of determining prognosis for patients with CLL, it fails to identify the substantial subset of patients with early-stage CLL who are likely to experience rapid progression to advanced disease. The use of LDT and new molecular-based laboratory tests (FISH, CD38) can identify patients with early-stage CLL who are at high risk of early progression.²⁸ We routinely perform CD38 testing and FISH testing for all pa-
Figure 2. Prognostic work-up for patients diagnosed as having chronic lymphocytic leukemia (CLL). CBC = complete blood cell count; FISH = fluorescence in situ hybridization; LDT = lymphocyte doubling time.

Patients with newly diagnosed CLL to improve our ability to counsel such patients, identify individuals who may benefit from a shorter follow-up interval, and identify patients who may be candidates for participation in clinical trials of early intervention. The prognostic work-up for patients with CLL is summarized in Figure 2. Evaluation of Ig V\textsubscript{H} gene mutational status should be performed if clinically available at your medical center. In the future, other molecular markers may further improve our ability to identify patients with more aggressive disease.

**PATIENT FOLLOW-UP AND INDICATIONS FOR TREATMENT**
Currently, no known curative therapy exists for patients with CLL. Historically, the goals of treatment have been limited to alleviating disease-related symptoms and prolonging survival. Chemotherapy for all (nonselected) patients with early-stage CLL is associated with toxicity and no increase in survival; such treatment is not recommended outside of clinical trials.\textsuperscript{54,55} Watchful waiting with active supportive care measures (discussed subsequently) remains the standard of care for all patients with asymptomatic early-stage disease. If immediate treatment is not required, we initially monitor patients every 3 to 6 months for the first year (and every 6-12 months thereafter) to provide supportive care, assess change in lymphadenopathy, calculate LDT, and monitor for cytopenias. We maintain a 6-month follow-up period for individuals with high-risk features (CD38+; 17p– or 11q– by FISH); however, this interval can be lengthened to annual follow-up for patients
Consensus guidelines of the indications for treatment of patients with CLL have been published and are outlined in Table 4. Unlike acute leukemia, symptoms related to hyperviscosity or lymphocyte aggregation due to markedly elevated ALCs are extremely rare in CLL, and patients do not require treatment for an increased ALC alone (there is no ALC that necessitates treatment in and of itself).

The markedly shorter survival of some patients with early-stage disease (unfavorable chromosomal findings by FISH testing, nonmutated Ig V_H genes, high CD38 expression) and the introduction of less toxic biologic therapies have led numerous medical centers to explore the role of treatment for selected, high-risk patients with asymptomatic early-stage disease. Patients with these unfavorable features who have good performance status, particularly individuals with a life expectancy greater than 5 years, should be offered participation in clinical trials.

### TREATMENT OPTIONS

**Previously Untreated Patients**

For individuals requiring treatment, alkylator therapy with oral chlorambucil or intravenous cyclophosphamide is generally well tolerated with minimal to moderate myelosuppression in most patients. The overall (25%-35%) and complete (2%-10%) response rates are lower than with newer therapies; however, the overall survival is similar to that achieved with monotherapy with fludarabine. Over the past 10 to 15 years, treatment of CLL has been advanced by use of purine nucleoside analogues (fludarabine, pentostatin, and cladribine) used alone or in combination. Fludarabine alone is associated with a 60% to 70% response rate, of which 20% to 30% are complete responders. Compared with chlorambucil, there is evidence of improved progression-free survival with fludarabine; however, there is no difference in overall survival because patients who relapse after chlorambucil can be treated with fludarabine. Because of an increased incidence of severe autoimmune hemolytic anemia in patients treated with fludarabine, we perform Coombs testing before treatment and avoid fludarabine in all patients with positive results on Coombs testing or a history of hemolytic anemia.

Compared with chlorambucil, treatment with purine nucleoside analogues is associated with increased incidence of opportunistic infections due to its associated lymphopenia and neutropenia. Infections occurring in patients treated with fludarabine include an increased incidence of Pneumocystis carinii pneumonia, herpes family virus infections (herpes simplex virus, varicella zoster, and cytomegalovirus), and other opportunistic organisms. Prophylaxis for P carinii pneumonia (eg, sulfamethoxazole/trimethoprim) and herpes (eg, acyclovir) is recommended for all patients treated with fludarabine.

More recently, the development of monoclonal antibodies has led to use of chemoimmunotherapy with purine nucleoside analogues (fludarabine or pentostatin) combined with rituximab (anti-CD20 monoclonal antibody) with or without cyclophosphamide. These combinations have been associated with a high response rate (80%-90%) and an increased complete response rate (50%-60%). No published controlled trials have compared chemotherapy and chemoimmunotherapy, but data suggest an increased progression-free survival rate compared with historical studies of fludarabine monotherapy.

### Table 4. National Cancer Institute Criteria for Treatment*

<table>
<thead>
<tr>
<th>Indication for treatment</th>
<th>Exception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening anemia (hemoglobin, &lt;10.5 g/dL), thrombocytopenia (platelets, &lt;100 × 10^9/L) due to marrow failure</td>
<td>Rule out autoimmune hemolytic anemia, pure red blood cell aplasia, or ITP as etiology of cytopenias</td>
</tr>
<tr>
<td>&gt;50% increase in ALC in &lt;2 mo or anticipated lymphocyte doubling time of &lt;6 mo</td>
<td>Exclude acute infection or transient reactive etiology as cause of increase in ALC</td>
</tr>
<tr>
<td>Progressive or massive splenomegaly (&gt;6 cm below costal margin)</td>
<td>Consider Richter transformation if rapid enlargement</td>
</tr>
<tr>
<td>Progressive or massive lymphadenopathy (&gt;10 cm in longest dimension)</td>
<td>Consider Richter transformation if rapid enlargement</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>Exclude infection as the etiology of constitutional symptoms</td>
</tr>
<tr>
<td>Weight loss &gt;10% body weight in &lt;6 mo</td>
<td></td>
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<tr>
<td>Fever &gt;38°C for &gt;2 wk without infection</td>
<td></td>
</tr>
<tr>
<td>Night sweats without evidence of infection</td>
<td></td>
</tr>
<tr>
<td>Extreme fatigue (unable to work or perform usual activities)</td>
<td></td>
</tr>
<tr>
<td>Autoimmune anemia or ITP poorly responsive to other therapies</td>
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</tbody>
</table>

*ALC = absolute lymphocyte count; ITP = idiopathic thrombocytopenic purpura.
ongoing clinical studies are evaluating the efficacy of these combinations.

Our current practice is to offer chemoimmunotherapy (fludarabine or pentostatin and rituximab with or without cyclophosphamide) as initial treatment for patients with good performance status along with infection prophylaxis (sulfamethoxazole/trimethoprim and acyclovir) as described previously. Oral chlorambucil is a useful treatment, especially in very elderly patients or in those with poor performance status.

**Relapsed or Refractory Disease**

Given that CLL is rarely curable, many patients develop symptoms of recurrence that requires additional treatment. Selection of the optimal salvage treatment depends on patient age, performance status, response to prior therapy, duration of remission, adverse effects with prior treatment, and comorbid illness. Treatment options include purine nucleoside analogues (fludarabine, pentostatin), alkylating agents (chlorambucil, cyclophosphamide), monoclonal antibody–based treatment, stem cell transplantation, combinations of these treatments, and experimental treatments. Alemtuzumab, a Food and Drug Administration–approved monoclonal antibody for recurrent or refractory disease that targets CD52, has demonstrated significant activity in such patients. Treatment protocols using alemtuzumab as first-line therapy and in combination with chemotherapy or other antibody-based therapies are in development.

**Role of Stem Cell Transplantation in CLL**

Stem cell transplantation is a proven, effective treatment strategy for several hematologic malignancies. Autologous stem cell transplantation enhances treatment by permitting larger doses of chemotherapy (dose intensification), whereas allogeneic transplantation has the potential to provide an immune-mediated antileukemic effect (graft vs leukemia effect) in addition to dose intensification. No randomized controlled trials comparing marrow transplantation to conventional chemotherapy have been performed in patients with CLL. Early results from trials of autologous marrow transplantation in patients with CLL failed to show a plateau in survival curves and suggest this therapy is not curative in CLL. Although early results of trials of allogeneic transplantation in CLL suggest a plateau in the survival curve, these studies have been associated with a high treatment-related mortality. Several ongoing trials are exploring nonmyeloablative allogeneic transplantation for CLL to determine whether this approach is a less toxic method to achieve the benefits of allogeneic transplantation. In younger patients with recurrent or high-risk (eg, 17p– by FISH) disease, referral to a transplantation center should be considered so that the role of transplantation as a salvage therapy can be assessed or the patient can have an opportunity to undergo early transplantation as part of a clinical trial. The optimal conditioning regimen, source of stem cells, and timing of cell transplantation in patients with CLL have yet to be defined.

**DISEASE-RELATED COMPLICATIONS AND SUPPORTIVE CARE GUIDELINES**

Patients with CLL are at increased risk for numerous disease-related complications including infections, autoimmune diseases, secondary malignancy, and transformation to large B-cell non-Hodgkin lymphoma (Richter transformation) or Hodgkin lymphoma.

Individuals with CLL have an increased incidence of bacterial, fungal, and viral infections due to the hypogammaglobulinemia associated with CLL and the neutropenia and T-cell deficiencies associated with CLL chemotherapy. All patients with CLL should be offered a pneumococcal vaccination at diagnosis (and every 5 years) and annual influenza vaccination. Patients with multiple recurrent infections and hypogammaglobulinemia may benefit from prophylactic immunoglobulin infusions at a dosage of 0.3 g/kg intravenous every 4 to 6 weeks. Cytomegalovirus infection should be considered in the differential diagnosis of fever in all patients with CLL who have been treated with fludarabine (other purine analogues) or alemtuzumab.

Autoimmune hemolytic anemia (4%-11% of patients with CLL) and idiopathic thrombocytopenic purpura (ITP) (2%-4% of patients with CLL) are the most common autoimmune diseases in patients with CLL. Cases of pure red blood cell aplasia (1%-5% of patients with CLL) and acquired angioedema due to C1Q esterase deficiency are also observed. These autoimmune complications can occur independent of the stage of disease. A bone marrow biopsy can be helpful in evaluating anemia and distinguishing hemolytic anemia or pure red blood cell aplasia from progressive CLL. Treatment of autoimmune hemolytic anemia and ITP may include corticosteroids, intravenous γ-globulin, rituximab, and splenectomy. Depending on the patient’s clinical scenario, response to treatment, and stage of disease, treatment of these autoimmune complications may also require treatment of CLL (eg, chemotherapy).

Patients with CLL are also at increased risk for developing secondary malignancy, especially nonmelanomatous skin cancer. Normally indolent cutaneous malignancies, especially some cases of squamous cell carcinoma of the skin, may behave extremely aggressively in patients with CLL. Counseling about sun protection and regular skin examinations are warranted for all patients with CLL. Solid tumors also appear to be more common in patients with CLL. One recent study found a 3-fold increase in the risk of second malignancies (other than nonmelanomatous skin...
cancer) in patients with CLL compared with age-matched controls. Maintaining active preventive screening according to established guidelines (mammography, colonoscopy, prostate-specific antigen testing) is crucial, especially in asymptomatic patients with low-stage disease.

Of patients with B-cell CLL, 5% to 8% experience transformation to a diffuse, large B-cell non-Hodgkin lymphoma (Richter transformation). Transformation is frequently accompanied by increased B-type symptoms (fever, night sweats, weight loss), rapid increase in nodal size, and increased lactate dehydrogenase level. Richter transformation requires aggressive chemotherapy such as CHOP (cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin [vincristine], and prednisone)–containing regimens similar to those used to treat de novo diffuse large B-cell lymphoma.

**RECOMMENDATIONS AND FUTURE DIRECTIONS**

Over the past 2 decades, substantial changes have occurred in the precision of diagnosis, stage at diagnosis, accuracy of prognostic tools, treatment options, and supportive care measures for patients with CLL. The primary care provider plays the central role in diagnosis, follow-up, and appropriate referral of these patients. The fact that more than one half of patients with early-stage CLL will eventually need treatment for CLL, coupled with improvements in our ability to identify and counsel high-risk patients with early-stage disease, suggests that a hematology consultation should be considered for all patients at diagnosis. Although watchful waiting is the cornerstone of management for most asymptomatic patients with early-stage disease, clinical trials for selected patients with markers of biologically aggressive disease are under way. Targeted biologic therapies have expanded treatment options and improved response rates for patients with CLL. Improvements in our understanding of disease-related complications have led to refinements in supportive care guidelines. Application of these advances in diagnosis, prognostication, treatment, and supportive care can improve the quality of life for patients with CLL.

We are grateful to Neil Kay, MD, and Clive Zent, MD, for their critical review of the submitted manuscript and to William Morice, MD, for his review of Table 1.

**REFERENCES**


79. Kyasa MJ, Hazlett L, Parrish RS, Schichman SA, Zent CS. Veterans with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) have a markedly increased rate of second malignancy, which is the most common cause of death. Leuk Lymphoma. 2004;45:507-513.

Questions About CLL

1. Which one of the following indicates the percentages of patients with early-stage CLL who are likely to experience early disease progression and death due to CLL?
   a. 10%
   b. 25%
   c. 50%
   d. 75%
   e. 90%

2. Which one of the following is the result of treatment of nonselected asymptomatic patients with early-stage CLL?
   a. Prolonged overall survival
   b. Increased risk of Richter transformation
   c. Prevention of infectious complications
   d. Decreased autoimmune complications
   e. Increased toxicity

3. Which one of the following is not a frequent complication experienced by patients with CLL?
   a. Second malignancy
   b. Autoimmune disease
   c. Stroke when ALC is >200 × 10^9/L
   d. Infections due to hypogammaglobulinemia
   e. Infections due to defects in cell-mediated immunity

4. Which one of the following is not an accepted indication for treatment in patients with CLL?
   a. Anemia due to bone marrow failure
   b. >50% increase in ALC in <2 months
   c. ITP due to marrow failure
   d. ALC >200 × 10^9/L
   e. Autoimmune hemolytic anemia poorly responsive to corticosteroid therapy

5. Which one of the following is not a currently recommended supportive care guideline for all patients with CLL?
   a. Pneumococcal vaccination
   b. γ-Globulin replacement
   c. Screening for secondary malignancies
   d. Monitoring for autoimmune disease
   e. Annual influenza vaccination