Chronic Lymphocytic Leukemia: Diagnosis and Treatment

Paolo Strati, MD; Nitin Jain, MD; and Susan O’Brien, MD

Abstract

The complexity of the treatment of patients with chronic lymphocytic leukemia has increased substantially over the past several years as a consequence of the advent of novel biological agents such as ibrutinib, idelalisib, and venetoclax, as well as increasingly potent anti-CD20 monoclonal antibodies. In addition, the identification of molecular predictive markers and the introduction of more sensitive and sophisticated techniques to assess minimal residual disease have allowed optimization of the use of chemotherapeutic and targeted therapies and may become standard of care in the future. This review summarizes the diagnosis, prognostic, and treatment of patients with chronic lymphocytic leukemia with emphasis on new prognostic and predictive factors and novel treatment strategies.
introduction of more sensitive and sophisticated techniques to assess minimal residual disease (MRD). This review summarizes the diagnosis, prognostication, and treatment of patients with CLL with emphasis on new prognostic and predictive factors and novel treatment strategies.

**EPIDEMIOLOGY**

Chronic lymphocytic leukemia is the most common adult leukemia in the Western World, accounting for nearly 25% of all leukemias and 1.3% of all cancers. Its incidence is substantially lower among Asian individuals and higher among Ashkenazi Jews. Based on 2012-2014 data, approximately 0.6% of US men and women will be diagnosed with CLL at some point during their lifetime. Between 2010 and 2014, the number of new cases of CLL in the United States was 4.7 per 100,000 men and women per year, and in 2017, up to 20,110 new cases are estimated. The incidence and prevalence of CLL are similar in Europe. Chronic lymphocytic leukemia predominantly affects older individuals, with more than 70% of patients being older than 65 years; the median age at diagnosis is 72 years. Males and whites are more frequently affected than females (male to female ratio, 1.5-2:1) and other races.

**ETIOLOGY**

A genetic predisposition for CLL is suggested by family studies, with a higher prevalence of disease observed among relatives of patients with sporadic CLL, and up to 6 single-nucleotide polymorphisms known to confer an increased risk for development of CLL in large case-control series. Recently a whole-genome sequencing study reported that CLL mutations can be attributed to 3 key mutational processes: 2 types of activation-induced cytidine deaminase signatures and an aging signature, operating at different times throughout CLL evolution. The frequency of CLL progressively increases with age, suggesting that a persistent exposure to a self- or non-self-antigen may also be a predisposing factor. Of interest, among patients with hepatitis C, the incidence of CLL is significantly higher than that in the general population; studies to determine whether specific antigenic stimuli can lead to the development of CLL are ongoing and may shed light on its pathogenesis and natural history. Although individuals living on farms or exposed to Agent Orange are at higher risk for development of CLL and sun exposure protects from its onset, a clear association between CLL and exposure to ionizing radiation has never been proven.

**CLINICAL PRESENTATION**

Patients with CLL have varied clinical presentations. Most patients are asymptomatic and CLL is diagnosed only because of an incidental finding of lymphocytosis on a routine complete blood cell count; this symptom can be accompanied to a variable degree with anemia and/or thrombocytopenia. In some cases, patients also can have palpable lymphadenopathy and/or hepatosplenomegaly, which in rare cases can produce symptoms secondary to local compression. Extranodal and/or extramedullary presentations of CLL rare, with the skin and central nervous system being the most frequent sites of involvement. A minority of patients will present with constitutional symptoms, defined as persistent fever, night sweats, and/or unintentional weight loss, while fatigue is a common symptom. Finally, CLL can be diagnosed as a consequence of clinical signs and symptoms secondary to its complications rather than to its direct involvement, including autoimmune disease, infections, or second cancers (see “Complications” section).

**DIAGNOSIS**

The definition of CLL was first established by the National Cancer Institute Working Group in 1996 and was then modified by the International Workshop on CLL (iwCLL) in 2008. The latter definition has not been revised substantially in the latest World Health Organization classification of lymphoid neoplasms. The diagnosis of CLL requires the presence of at least 5 x 10^9/L B lymphocytes in the peripheral blood and of a clonal B-cell population, detected by flow cytometry, positive for light chain restriction (either k or λ), CD5, CD23, CD79b, and surface immunoglobulin expression, and low levels of CD20; under simple microscopic examination, CLL cells have a typical appearance of smudge cells, which are artifacts from lymphocytes damaged during the slide preparation. Rarely,
CLL cells can have an atypical morphology, defined as more than 15% of cells with cleaved nuclei and/or lymphoplasmacytoid features, and an atypical immunophenotype, with a modified Matutes score of less than 4 (based on atypical expression of CD5, CD23, FMC7, surface immunoglobulin, CD22, and/or CD79b); this entity is sometimes referred to as atypical or variant CLL.24-27 The main entities that should be included in the differential diagnosis for CLL are mantle cell lymphoma (MCL), splenic marginal zone lymphoma, and B-cell prolymphocytic leukemia. The detection of t(11;14) by chromosome band analysis of fluorescence in situ hybridization (FISH) allows differentiation of MCL from CLL. As opposed to CLL, splenic marginal zone lymphoma is rarely positive for CD23, whereas it can be positive for CD5 in 5% to 10% of cases, and invariably never involves the bone marrow. Finally, B-cell prolymphocytic leukemia presents with more than 55% prolymphocytes in the peripheral blood and is positive for CD5 but negative for CD23. The characterization of other lymphoproliferative disorders, rarely overlapping with CLL, is beyond the scope of this review.28

When a clonal B-cell population is detected in enlarged lymph nodes in absence of peripheral clonal lymphocytes, the term small lymphocytic lymphoma should be used, identifying a clinical variant of the same histopathologic entity.18 The presence of a clonal B-cell population in the peripheral blood with fewer than 5 × 10^9/L B cells and no other signs of a lymphoproliferative disorder identifies a third entity called monoclonal B-cell lymphocytosis, initially defined in 2005 by the International Familial CLL Consortium and later acknowledged by the iwCLL.29

A bone marrow biopsy is not required to diagnose CLL but can be pursued in the presence of anemia and/or thrombocytopenia to differentiate between autoimmunity and myelophthisis, with therapeutic implications (see “Indications for Treatment” section).

**PROGNOSIS**

Given the considerable heterogeneity in clinical outcome for patients with CLL, several efforts have been made to identify prognostic factors in order to better counsel patients with newly diagnosed disease. The first prognostic tool for patients with CLL was provided more than 4 decades ago by Rai and Binet, who developed 2 separate staging systems—today associated with their names—based on simple clinical parameters, such as complete blood cell count and physical examination; the 5 stages identified by Rai and the 3 stages identified by Binet clearly associate with differential clinical outcome, as repeatedly confirmed over the past 40 years (Table 1).30,31 Subsequently, other easily measurable parameters, such as absolute lymphocyte count doubling time and bone marrow invasion pattern, were suggested to be useful prognostic markers, but their power has been found to be limited.32,33

More robust prognostic markers are provided by newer techniques, such as immunoenzymatic assays, flow cytometry, cytogenetics, and molecular biology. Serum parameters, measured by simple immunoenzymatic assays, include β2-microglobulin (B2M) and thymidine kinase levels; a B2M level of more than 3.5 mg/L and a thymidine kinase level higher than 8.5 U/L have both been reported to be associated with higher disease burden and shorter survival.34-36 The 3 most commonly employed flow cytometry-based prognostic markers are CD38 and ZAP70 (which are proteins involved in the B-cell receptor signaling) and CD49d (a surface integrin); CD38 expression (defined as ≥30% of positive cells), ZAP70 expression (>20% of cells), and CD49d expression (≥30%) on CLL cells each is in fact independently associated with shorter survival.37-42 Of interest, the latter may also be associated with lymphadenopathy.43

Given the low mitotic rate of CLL cells, FISH, as opposed to conventional chromosome

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**TABLE 1. Rai and Binet Staging Systems for Chronic Lymphocytic Leukemia**

<table>
<thead>
<tr>
<th>Rai stage</th>
<th>Binet stage</th>
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<tbody>
<tr>
<td>0</td>
<td>A &lt;3 Lymphadenopathies</td>
</tr>
<tr>
<td>I</td>
<td>B ≥3 Lymphadenopathies</td>
</tr>
<tr>
<td>II</td>
<td>I Anemia (hemoglobin &lt;11 g/dL)</td>
</tr>
<tr>
<td>III</td>
<td>C Hemoglobin &lt;10 g/dL and/or platelet count &lt;100 × 10^9/L</td>
</tr>
<tr>
<td>IV</td>
<td>IV Thrombocytopenia (platelet count &lt;100 × 10^9/L)</td>
</tr>
</tbody>
</table>

*SI conversion factors: To convert hemoglobin values to g/L, multiply by 10.0.*
Progressive lymphocytosis (doubling time

Progressive hepatomegaly or splenomegaly

Progressive lymphadenopathies (at least 10 cm)

Progressive bone marrow failure: anemia and/or thrombocytopenia

Progressive constitutional symptoms

**TABLE 2. Indications for Treatment Initiation in Chronic Lymphocytic Leukemia**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Treatment indication</th>
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<tbody>
<tr>
<td>Progressive constitutional symptoms</td>
<td></td>
</tr>
<tr>
<td>Progressive bone marrow failure; anemia and/or thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Progressive lymphadenopathies (at least 10 cm)</td>
<td></td>
</tr>
<tr>
<td>Progressive bone marrow failure; anemia and/or thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Progressive hepatomegaly (doubling time &lt;6 months)</td>
<td></td>
</tr>
<tr>
<td>Steroid-refractory autoimmune hemolytic anemia and/or immune thrombocytopenia</td>
<td></td>
</tr>
</tbody>
</table>

Steroid-refractory autoimmune hemolytic anemia and/or immune thrombocytopenia

by polymerase chain reaction–based techniques, with TP53 (for expansion of gene symbols, use search tool at www.genenames.org) mutation (most commonly seen with deletion 17p) and ATM mutation (most commonly observed with deletion 11q) associated with shorter survival. Next-generation sequencing has identified additional mutations with prognostic importance, including NOTCH1, SF3B1, MYD88, and BIRC3, but their validation is ongoing and application to common practice is impaired by the limited availability of such techniques. The degree of somatic mutation in the immunoglobulin heavy chain variable gene (IGHV) is prognostic, with unmutated IGHV (defined as <2% difference from germline nucleotide sequence) associated with worse outcome. IGHV mutation status testing is preferred over flow cytometry; in fact, while CD38 and ZAP70 can be used as surrogate markers of IGHV status, their assessment is challenging and results can vary among different laboratories or at different time points in the natural history of CLL. Finally, at least one-third of patients with CLL have stereotyped B-cell receptors, sharing quasi-identical binding sites; these receptors are associated with specific outcomes, but techniques used to detect them are not widely available, and as a consequence, stereotyped B-cell receptors are rarely assessed in clinical practice.

Several efforts have been made to integrate all the prognostic factors outlined previously into a single prognostic score. A recent systematic review and meta-analysis has reported that published evidence is sufficient to recommend that FISH and IGHV analysis be performed as standard clinical tests for all patients with newly diagnosed CLL in those countries with the resources to do so. In addition, the CLL international prognostic index was formulated on the basis of age, B2M levels, Rai stage, presence of del17p by FISH (or TP53 mutation), and IGHV mutational status; this scale was validated by Mayo Clinic as well as in a Scandinavian population. Use of a prognostic score, however, is not yet recommended in the iwCLL guidelines; of interest, such scores do not incorporate comorbidities, an important factor in the clinical course of patients with CLL given their median age at diagnosis (72 years). In addition to prognostication, many of these markers may also have a predictive value and guide treatment decisions (see “Treatment” section).

**INDICATIONS FOR TREATMENT**

Not all patients with CLL require treatment at the time of diagnosis, and most patients can undergo active surveillance for many years before treatment is needed. Indications for treatment are detailed in the 2008 iwCLL guidelines and are mainly based on 3 elements: symptoms, complete blood cell count, and physical examination findings (Table 2).

Constitutional symptoms, defined as persistent and unexplained fever (temperature >38°C) and/or weight loss (>10% of the baseline weight over the course of less than 6 months) and/or severe night sweats, can represent a first indication for treatment.

Progressive lymphocytosis, hemoglobin level less than 10 g/dL, or platelet count less than 100 x 10^9/L represents another indication
for treatment; of interest, rather than the absolute number of lymphocytes, it is the lymphocyte doubling time that is noted in the guidelines (rapid doubling is <6 months). In addition, in presence of anemia and/or thrombocytopenia, an autoimmune etiology must always be ruled out, and only refractory autoimmune hemolytic anemia (AIHA) and/or immune thrombocytopenia (ITP) would prompt CLL-specific therapy initiation. Finally, treatment is recommended in the presence of progressive and/or symptomatic lymphadenopathy (>10 cm) and/or hepatosplenomegaly. It is important to highlight that lack of data to support early intervention in CLL derives from the chemoimmunotherapy era, and several ongoing trials are addressing this dogma, particularly in high-risk patients, with use of the less toxic novel agents such as ibrutinib (ClinicalTrials.gov Identifiers: NCT03207555, NCT02863718, NCT02518555).

**ASSESSMENT OF RESPONSE**

Response assessment is detailed in the iwCLL 2008 guidelines,22 although their timing and validity may be challenged by the advent of the new biological agents. Based on the experience from the chemoimmunotherapy era, response should be assessed 2 to 3 months after the completion of therapy and should be based on complete blood cell count, physical examination findings, and bone marrow biopsy; computed tomography is not recommended outside of clinical trials. Criteria to assess response to treatment are summarized in Table 3. Of interest, the clinical benefit of complete remission (CR) with incomplete bone marrow recovery seems to be comparable to that of CR.66 If criteria for CR are met but the bone marrow includes lymphocytic nodules, the recommended term is nodular partial remission, the prognosis of which is more similar to that of partial remission.67

Over the past several years, the eradication of MRD, measured by 4-color flow cytometry with a sensitivity of less than 0.01%, has increasingly gained importance. In particular, achievement of negative MRD status after chemoimmunotherapy has been prospectively associated with prolonged progression-free survival (PFS) and overall survival (OS), with retrospective evidence that early eradication may prompt treatment discontinuation.67,68 However, similar data have not yet been obtained with newer agents such as ibrutinib, idelalisib, and venetoclax, and MRD monitoring and achievement is not recommended by standard guidelines.

**TREATMENT**

The treatment of patients with CLL has undergone substantial advances over the past several years, although the optimal management of high-risk groups, particularly patients with relapsed disease who have deletion 17p, remains a major challenge. A treatment strategy flow chart is proposed in the Figure. Some of the prognostic factors outlined previously, such as deletion 17p (or TP53 mutation), IGHV mutation status, and complex cytogenetics have increasingly been shown to have

### TABLE 3. Treatment Response Criteria\textsuperscript{a,b,c}

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Complete remission</th>
<th>Partial remission</th>
<th>Progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>None &gt;1.5 cm</td>
<td>≥50% Decrease</td>
<td>≥50% Increase</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>None</td>
<td>≥50% Decrease</td>
<td>≥50% Increase</td>
</tr>
<tr>
<td>Marrow lymphocytes</td>
<td>&lt;4000/μL</td>
<td>≥50% Decrease</td>
<td>≥50% Increase</td>
</tr>
<tr>
<td>Blood lymphocytes</td>
<td>&lt;30%</td>
<td>≥50% Decrease</td>
<td>≥50% Increase</td>
</tr>
<tr>
<td><strong>Group B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>&gt;1.5 × 10(^9)/L</td>
<td>≥50% Increase</td>
<td>NA</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&gt;11 g/dL</td>
<td>≥50% Increase</td>
<td>≥2 g/dL Decrease</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&gt;100 × 10(^9)/L</td>
<td>≥50% Increase</td>
<td>≥50% Decrease</td>
</tr>
</tbody>
</table>

\(\text{SI conversion factors: To convert hemoglobin values to g/L, multiply by 10.0.}\)

\(\text{NA} = \) not applicable.

\(\text{For complete remission, all criteria must be met. For partial remission, at least 2 criteria from group A and 1 from group B must be met.}\)

The term stable disease is used when none of the 3 response category definitions are met.
predictive value, and their assessment may guide the treatment decision.

**Initial Therapy**

The decision about optimal frontline therapy for patients with CLL is based on several factors, including both the patient’s fitness and disease biological features. Fit patients, defined in the United States as patients younger than 65 years and with a good performance status and in Europe as patients with a creatinine clearance of 70 mL/min or greater and a comorbidity index rating scale score of 6 or less, are good candidates for chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR). Frontline treatment with FCR is associated with a response rate of 90% to 95% and a CR rate of 40% to 75%. Typically, 6 cycles are given, and early discontinuation based on achievement of MRD eradication has not yet been prospectively proven effective. Prolonged myelosuppression, early and late infections, and second cancers still remain the main concerns with the use of this regimen, and better tolerability has been described with the combination of bendamustine and rituximab (BR). The latter regimen should be considered in older patients, in whom BR has been found to have efficacy comparable to that of FCR. In a phase 3 trial comparing FCR to BR as frontline treatment for patients with CLL, the use of BR produced a shorter median PFS (42 vs 55 months); however, among patients older than 65 years, no difference in PFS was observed, despite significantly increased infectious complications with the use of FCR.

Recent long-term follow-up has demonstrated that chemoimmunotherapy may be curative in a subset of patients, identified by the absence of unmutated IGHV and deletion 17p (or TP53 mutation). Three different studies have reported that in patients without deletion 17p, the use of frontline FCR is associated with a significantly prolonged PFS and OS in the presence of mutated IGHV compared with that seen in patients with unmutated IGHV, with more than half of the former patients still disease free after a median follow-up of more than 10 years.

For patients with deletion 17p or TP53 mutation, the long-term results with chemoimmunotherapy are suboptimal. For these patients, ibrutinib, an oral selective and irreversible inhibitor of the Bruton tyrosine kinase (BTK), is the current standard treatment. Bruton tyrosine kinase is a kinase in the B-cell receptor signaling pathway and is required for normal B-cell function and development.
phospholipase Cγ2, leading to activation of downstream signaling pathways. Ibrutinib irreversibly binds to BTK at the cysteine residue C481, preventing kinase activity and blocking downstream signaling pathways. Ibrutinib also disrupts the interaction between the CLL clone and the bone marrow microenvironment, inducing further apoptosis. Most of the clinical data regarding the efficacy of ibrutinib derives from studies including patients with relapsed CLL. In a phase 1b study of ibrutinib as initial therapy for 31 older patients with CLL and in a phase 2 study of ibrutinib as frontline treatment for 35 patients with deletion 17p CLL, ibrutinib produced high response rates (84%-97%) but CR rates of only 12% to 23%, with most patients achieving either a partial remission (mostly because of persistent bone marrow disease) or a partial remission with a lymphocytosis (likely as a consequence of its mechanism of action, aimed at blocking the interaction between CLL cells and their niche). Nevertheless, patients had prolonged PFS and OS, including those with deletion 11q, deletion 17p, and/or unmutated IGHV. Ibrutinib is associated with adverse effects, the most prominent being hypertension, atrial fibrillation, musculoskeletal pain, diarrhea, bleeding, and drug-drug interaction.

In frail patients, treatment can still be administered because most patients tolerate it well. For this population, frontline treatment can be given with a combination of chlorambucil and an anti-CD20 monoclonal antibody; with the use of rituximab, the overall response rate (ORR) is 82% to 84%, and median PFS is 24 to 35 months. Similar results have been observed with chlorambucil combined with more novel monoclonal antibodies, such as ofatumumab (ORR, 82%; PFS, 23 months) or obinutuzumab (ORR, 78%; PFS, 29 months). In very frail patients with multiple comorbidities, treatment with single-agent anti-CD20 monoclonal antibody can be considered, although lower ORR and shorter PFS should be expected.

In a clinical trial of frontline therapy in older patients with CLL (RESONATE 2 [a multicenter, open-label, randomized phase 3 trial (study number, PCYC-1115-CA) to evaluate the efficacy and safety of single-agent ibrutinib as compared with chlorambucil in patients 65 years of age or older with previously untreated CLL] and no deletion 17p, ibrutinib was superior to chlorambucil in terms of response rate, survival, and toxicity. Although a direct comparison between ibrutinib and the combination of chlorambucil and obinutuzumab has not yet been reported, the PFS data with ibrutinib monotherapy suggests that ibrutinib is superior to any chlorambucil-based therapy. Ibrutinib is an appropriate frontline regimen for patients who are not eligible for chemoimmunotherapy based on clinical fitness and is the recommended regimen in the presence of deletion 17p/TP53 mutation.

Therapy for Relapsed Disease

Despite recent progress, the treatment of patients with relapsed or refractory CLL remains an unmet need. One major challenge is that this population has numerous adverse factors, such unmutated IGHV and TP53 mutation. In fact, while at the time of diagnosis abnormalities in the short arm of chromosome 17 are reported in approximately 5% of patients by conventional cytogenetic testing and in up to 9% by FISH, in patients with relapsed and refractory disease the prevalence can be as high as 30% to 40% of patients. Although patients who experience relapse from 24 to 36 months after frontline chemoimmunotherapy can be safely rechallenged with the same regimen, their median PFS after salvage therapy is only 21 months; even more disappointing outcomes are observed with the use of salvage FCR in high-risk patients, such as those who have relapse within the first 3 years or those who have TP53 mutation and/or unmutated IGHV. Short-lasting responses are observed with ofatumumab, an agent approved for patients who experience relapse after chemoimmunotherapy or whose CLL is refractory to such treatment. Clearly, there is a need for therapies for patients with relapsed CLL.

The use of ibrutinib as salvage therapy has considerably changed the management and prognosis of patients with relapsed CLL. In a multicenter phase 1b/2 study, 101 patients with relapsed refractory CLL received salvage therapy with ibrutinib over the course of 5 years, 34% of whom had deletion 17p and 78% of whom had an unmutated IGHV. The
ORR was 86%, with 10% CR; the most frequent severe adverse events were hypertension, pneumonia, neutropenia, and atrial fibrillation, and treatment was discontinued because toxicity in 20% of cases. At most recent follow-up, median PFS was 52 months for the entire group; the median PFS for the deletion 17p subgroup was 26 months. In a subsequent randomized phase 3 study of ibrutinib compared with ofatumumab for the treatment of patients with relapsed CLL, 195 patients were assigned to the ibrutinib arm, 32% of whom had deletion 17p. The ORR was 90% in the ibrutinib arm and 25% in the ofatumumab arm. After a median follow-up of 19 months, the median PFS and median OS were not reached in the ibrutinib arm, and both were significantly prolonged compared with that seen in patients enrolled in the ofatumumab arm. Of interest, high-impact factors did not adversely affect outcomes with ibrutinib.

The most common options for patients who experience relapse after chemoimmunotherapy and/or ibrutinib are idelalisib (in combination with rituximab) and venetoclax. Idelalisib is a potent and selective inhibitor of PI3K-δ, a kinase downstream in the B-cell receptor signaling pathway; this pathway is constitutively activated in CLL cells. Idelalisib has been investigated in combination with rituximab in patients with relapsed refractory CLL and produced an ORR of 81%; the median PFS was reached after a relatively short follow-up. The main concern with the use of this agent is its toxicity profile, particularly the occurrence of colitis, hepatitis, pneumonitis, and rash; these adverse events may be immune mediated, and a more intact immune system seen in previously untreated patients may contribute to the higher incidence seen in that group. As a consequence, the use of idelalisib in the United States is currently limited to the relapse setting.

Venetoclax is a BH3 mimic targeting BCL2, a protein overexpressed in CLL. In a study of patients with relapse/refractory CLL treated with venetoclax, the ORR was 77%, although the population was heavily pretreated (median of 4 prior regimens), and 23% of patients achieved CR. The main adverse effects of venetoclax are neutropenia and tumor lysis syndrome; because of the latter, venetoclax is always given via a dose ramp-up schema, starting with 20 mg and achieving the target dose of 400 mg daily over 5 weeks. Patients at high risk for tumor lysis syndrome may need to be hospitalized during initial ramp-up. When combined with rituximab, venetoclax prolonged PFS compared with chemoimmunotherapy (bendamustine and rituximab) in a phase 3 trial of patients with relapsed/refractory CLL.

With extended follow-up, resistance to and/or intolerance of all of the aforementioned agents is being increasingly observed, and research aimed at identifying new therapeutic targets is ongoing. Whole-exome sequencing of 6 patients with CLL who had development of resistance to ibrutinib revealed mutations acquired in BTK at the binding site of ibrutinib (C481) with a cysteine to serine mutation, and several different mutations in phospholipase Cγ2, the kinase immediately downstream of BTK. Mechanisms of resistance to idelalisib and venetoclax have not yet been described, but potential pathways may include up-regulation of either PIK3CD or an alternative class 1A PI3K for the former and up-regulation of alternative antiapoptotic BCL2 family members, such as BCL-XL, BCL-W, MCL1, and BCL2A1 for the latter.

**Maintenance Therapy**

Treatments with antibodies such as rituximab and ofatumumab have been explored as consolidation strategies to prolong response duration, with moderate success. Lenalidomide is an oral immunomodulatory drug with activity in both treatment-naïve and relapsed CLL. The results of 2 randomized studies of lenalidomide as maintenance therapy have been recently reported, showing a significant prolongation in PFS compared with that seen with placebo, when used both after frontline or salvage therapy. The German CLL Study Group conducted a phase 3, double-blinded randomized study evaluating the efficacy of lenalidomide maintenance compared with placebo among patients who had residual disease after frontline FCR and had at least one unfavorable prognostic factor. The median PFS in the patients randomized to lenalidomide was significantly longer than that of patients randomized to the placebo arm,
with a relative risk reduction for progression of more than 80%. The second study of maintenance therapy with lenalidomide, reported by Foà et al, was a phase 3 randomized study of lenalidomide maintenance compared with placebo following second-line treatment. Assignment to the lenalidomide and placebo arms was based on response at the end of second-line treatment and the presence of adverse prognostic factors. The median PFS was significantly longer for patients treated with lenalidomide compared with those randomized to the placebo arm. In both studies, the rates of neutropenia and diarrhea were higher with lenalidomide than with placebo. In the future, when targeted therapy, currently used indefinitely, may become more frequent than the use of chemoimmunotherapy, a consolidation and/or maintenance strategy would become less relevant.

Role of Stem Cell Transplant
The advent of novel biological agents able to produce durable responses in high-risk patients is changing the treatment paradigm in CLL, considerably decreasing the number of patients evaluated for stem cell transplant (SCT). However, in absence of long-term follow-up data, allogeneic SCT should still be considered in fit patients with relapsed/refractory CLL and deletion 17p/TP53 mutation once remission is achieved with therapy. In fact, with the use of reduced-intensity conditioning regimens, early mortality has significantly decreased, but 5-year survival remains no higher than 60%, mostly because of non-disease-related mortality related to acute and chronic graft-vs-host disease.

COMPLICATIONS
Autoimmune Disorders
Patients with CLL have a dysregulated immune system, which can result in autoimmune complications. For unclear reasons, the most common autoimmune manifestations of CLL are hemolytic, with acquired angiodema, glomerulonephritis, and paraneoplastic pemphigus among the nonhematologic autoimmune complications. Autoimmune cytopenias occur in 4% to 10% of patients with CLL, with AIHA and ITP being the 2 most common. In the absence of clear CLL progression, AIHA and ITP can be treated, similar to their non-CLL-associated counterparts, with corticosteroids or rituximab. However, in the presence of concomitant progression or refractoriness, CLL treatment is warranted. Historically, there was concern that the use of fludarabine might exacerbate autoimmune cytopenias, likely by depleting regulatory T cells. As a consequence, non-fludarabine-containing regimens were proposed for the treatment of these patients; however, such concern has diminished with the addition of rituximab to nucleoside analogues. Recently, ibrutinib has been suggested as a potential treatment for autoimmune cytopenias in CLL, but its use to date remains anecdotal.

Infections
Although the agents employed for the treatment of patients with CLL are frequently associated with infectious complications, given the humoral and cellular immunodeficiency seen in this disease, even treatment-naive patients are at increased risk for infections as compared with the general population. While the number and function of T cells are not routinely monitored, immunoglobulin levels are easily obtained: patients with hypogammaglobulinemia and bacterial infections may benefit from gamma globulin replacement. In addition, prophylactic replacement may be considered in patients with mild-moderate but frequent infections. In light of the pathogenic mechanisms outlined previously, patients with CLL should be approached as high-risk patients when receiving counseling regarding influenza, pneumococcal infections, and tetanus, diphtheria, and acellular pertussis vaccines despite their hampered ability to mount an effective immunity in response to them; in addition, live attenuated vaccines should be avoided.

Second Cancers
Second cancers are present at the time of CLL diagnosis in 15% to 18% of patients and represent the ultimate cause of death in about 19% of affected individuals. Even among previously untreated patients, second cancers are more frequent than in the general population, particularly skin and prostate cancers, and tend to behave more aggressively.
Despite the evidence of association between CLL-specific features (such as presence of trisomy 12)\(^{126}\) and incidence of second cancers, the mechanism for such increased incidence is not fully understood, and it is likely to reside with CLL-associated immune defects. Patients with CLL should be counseled regarding the use of sun block and protective clothing and should undergo an annual skin examination. In addition, patients with CLL should also adhere to age-appropriate cancer screening, such as colonoscopy, mammograms, and cervical cancer screening.

**Richter Syndrome**

Richter syndrome is defined as the development of an aggressive lymphoma in a patient with previous or concomitant CLL; its histology is represented by diffuse large B-cell lymphoma in 95% of cases and Hodgkin lymphoma in 5%.\(^{134}\) The prevalence of RS has been estimated to be between 1% and 23%, increasing among patients with risk factors such as advanced Rai stage, diffuse lymphadenopathy, deletion 17p, trisomy 12, unmutated IGHV, and TP53 mutations.\(^{135}\) The median time of onset of RS is 2 to 6 years after the CLL diagnosis, and patients typically present with constitutional symptoms, diffuse bulky lymphadenopathy, and high lactate dehydrogenase levels. Positron emission–computed tomography characteristically reveals fluorodeoxyglucose-avid lymph nodes, and such findings are crucial in guiding biopsy for histologic confirmation of RS.\(^{136}\) The prognosis of patients with RS is dismal, particularly when clonally related to previous or concomitant CLL; in fact, cases of RS that do not have the same IGHV sequence as the previous or concomitant CLL clone occur in 20% of cases and behave like de novo diffuse large B-cell lymphoma, with frequent and durable responses to the combination of rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone.\(^{137}\) This regimen can produce an ORR of 67% in patients with clonally related RS, but median PFS is only 10 months, and more intensive chemotherapy regimens have failed to improve outcomes.\(^{137}\) Recently, responses have been reported with the use of checkpoint inhibition and with chimeric antigen receptor T-cell therapy.\(^{138,139}\) Finally, if remission is achieved, patients should receive with an allogeneic SCT, representing the only curative option for these patients.\(^{140}\)

**CONCLUSION**

The prognosis of patients with CLL has markedly improved over the past several years, with the advent of novel biological agents such as ibrutinib, idelalisib, and venetoclax. Although long-term follow-up data are still lacking, ibrutinib has slowly overcome chemotherapeutics as standard frontline treatment for fit patients with unfavorable prognostic features and for frail patients; venetoclax and the combination of idelalisib and rituximab are today among the most popular treatment options for patients who have relapse after ibrutinib treatment. New challenges are being seen, such as the management of agent-specific toxicities (eg, atrial fibrillation, colitis, tumor lysis) and the onset of resistance. Finally, despite the advent of immunotherapy, the treatment of patients with RS remains suboptimal, and research aimed at improving outcomes is ongoing.

**Abbreviations and Acronyms:** AIHA = autoimmune hemolytic anemia; B2M = β2-microglobulin; BR = bendamustine and rituximab; BTK = Bruton tyrosine kinase; CLL = chronic lymphocytic leukemia; CR = complete remission; FCR = fludarabine, cyclophosphamide, rituximab; FISH = fluorescence in situ hybridization; ITP = immune thrombocytopenia; iwCLL = International Workshop on CLL; MCL = mantle cell lymphoma; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RS = Richter syndrome; SCT = stem cell transplant

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