Abstract: Chronic lymphocytic leukemia (CLL) is a hematologic malignancy with a variable natural history that primarily affects older adults. Clinical, pathologic, and molecular factors have prognostic value in CLL and can assist in treatment planning. Once patients become symptomatic, they proceed to frontline therapy, which may include a variety of approaches depending on the patient’s circumstances. Chemoimmunotherapy is still often used for younger, fit patients, particularly those with lower-risk disease. Several CD20-targeting monoclonal antibodies have demonstrated efficacy in patients with CLL. Obinutuzumab and ofatumumab (both in combination with chlorambucil) have been approved by the US Food and Drug Administration (FDA) for first-line treatment. In March 2016, ibrutinib received FDA approval in the frontline setting and is now being used for many elderly or high-risk patients, providing an alternative to monoclonal antibodies administered alone or with chlorambucil. Although idelalisib has been evaluated in the frontline setting, combination trials have been halted based on reports of severe toxicities. Ongoing research aims to identify therapeutic approaches that yield deeper remissions that could persist after cessation of treatment.
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Initiation of Treatment in Chronic Lymphocytic Leukemia

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Chronic lymphocytic leukemia (CLL) is a relatively common hematologic malignancy, accounting for approximately a third of all leukemias worldwide. In the United States, approximately 15,000 cases of CLL were diagnosed in 2015, with a slight predominance in men vs women.\(^1\) Nearly 5000 deaths from CLL occur in the United States each year. Many patients live for years after their diagnosis, and thus the prevalence remains high.\(^1\) CLL predominantly affects older adults, with a median age at diagnosis of approximately 70 to 72 years.

**CLL Diagnosis and Staging**

The majority of patients diagnosed with CLL are asymptomatic. The diagnosis is often made incidentally when routine blood work reveals an elevated white blood cell count or absolute lymphocyte count. The diagnosis of CLL requires at least \(5 \times 10^9/L\) monoclonal B lymphocytes in peripheral blood, with clonality confirmed by flow cytometry.\(^2\) The leukemic cells are small, mature lymphocytes that are typically positive for CD5, CD23, CD19, and CD20.

In the United States, CLL is staged primarily using the Rai System, which categorizes the disease based on the presence of lymphocytosis (stage 0); enlargement of the lymph nodes (stage 1); enlargement of the spleen or liver (stage 2); anemia (stage 3); and thrombocytopenia (stage 4).\(^3\) Outside the United States, many clinicians use the Binet System, which categorizes CLL as stage A, B, or C based on hemoglobin level, platelet count, and number of enlarged areas.\(^4\) Most patients are diagnosed with early-stage CLL (Rai stage 0 or I), although some present with advanced-stage disease.

**Assessing Prognosis in CLL**

A variety of factors have been identified that contribute to prognosis in patients with CLL. Understanding a patient’s risk based on these factors has proven to be important not only for predicting prognosis but also for directing therapy. Relevant clinical and pathologic factors include clinical stage, tumor burden as reflected by bulky adenopathy, lymphocyte doubling time, and morphologic features, such as the presence of prolymphocytes, which could indicate that indolent disease has evolved to a more aggressive type. As in other ma-

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**Figure 1.** Chromosomal abnormalities are critically important to prognosis in patients with chronic lymphocytic leukemia. Adapted from Döhner H et al. *N Engl J Med*. 2000;343(26):1910-1916.\(^5\)

**Displacement**

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In recent years, it has been recognized that chromosomal abnormalities, which occur commonly in CLL, are critically important to prognosis. These aberrations are often detectable at diagnosis and can change or evolve over time. Some factors, such as del(13q), are associated with a favorable prognosis, whereas other factors, such as a complex karyotype, del(17p), del(11q), and TP53 mutations, are associated with a poor prognosis (Figure 1).3

Immunophenotypic markers can also predict survival in patients with CLL. Elevated expression levels of CD38 and ZAP-70 have both been associated with shorter survival (Figure 2).6 The mutational status of the immunoglobulin heavy-chain variable (IGHV) gene also has prognostic significance. CLL associated with mutated IGHV originates from a more mature cell and is thus associated with a more favorable outcome than unmutated IGHV-based CLL (Figure 3).6

Together, these clinical, pathologic, and molecular factors are used to gauge a patient’s risk. Low-risk patients are those with early-stage disease, a more nodular pattern of bone marrow infiltration, a longer lymphocyte count doubling time (>12 months), low CD38 and ZAP-70 expression, and more favorable chromosomal aberrations. Higher-risk patients include those with unfavorable chromosomal abnormalities and a rapidly progressive white blood cell count or doubling time. Novel gene mutations, such as those in NOTCH1 and SF3B1, are also beginning to be incorporated into CLL risk assessment. These factors are all important when categorizing patients with CLL into specific risk groups.

A new multivariate prognostic tool known as the CLL International Prognostic Index has shown higher discriminatory power than conventional staging systems. This index groups patients into 4 risk categories in which 5-year overall survival (OS) rates range from 19% to 95%.8

**Treatment Initiation and Selection in CLL**

Multiple factors contribute to the decision to initiate treatment in CLL and to the selection of therapy. They include patient-related factors, such as age, fitness, and treatment goals; disease-related factors, such as clinical stage, severity of symptoms, and genetic risk factors; and treatment-related factors, including prior therapies and responses to those therapies. Together, these factors are incorporated into the treatment decision-making process. A younger, fit patient with good renal function and few comorbidities may tolerate more aggressive treatment, termed “go-go” by the German CLL Study Group.10 In contrast, among patients who have an impaired physical condition, conservative therapy (termed “slow-go”) is more likely appropriate.10

Many patients with CLL do not require immediate treatment. Indications for the initiation of therapy include significant disease-related symptoms, threatened end-organ function, progressive bulky disease, progressive anemia, and progressive cytopenias.11 Among patients who lack a reason to initiate treatment, a watch-and-wait approach remains appropriate, even in the era of targeted therapies.

**Disclosure**

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Evolving Frontline Treatment in Chronic Lymphocytic Leukemia

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The initial treatment of CLL has evolved in recent years, from a strategy based on chemotherapy to one that includes immunotherapy and, in some patients, small-molecule targeted agents. The choice of a first-line regimen depends on multiple factors, including the patient’s age and general health, disease-related factors, and the patient’s individual treatment goals.

Conventionally, first-line therapy for older patients and those with significant comorbidities has included chlorambucil monotherapy, rituximab monotherapy, or a combination of chlorambucil and rituximab (a regimen used primarily outside the United States). For younger patients and those without significant comorbidities, combination chemoimmunotherapy regimens such as bendamustine and rituximab or fludarabine, cyclophosphamide, and rituximab (FCR) have largely become the standard of care for the initial treatment of CLL. These regimens have been thoroughly studied in clinical trials, and their safety profiles are well-established.

The randomized, phase 3 CLL10 trial compared the 2 common frontline CLL regimens, bendamustine/rituximab and FCR, in physically fit patients without del(17p). FCR was associated with superior efficacy but greater toxicity compared with the bendamustine and rituximab regimen. The median progression-free survival (PFS) was 55.2 months with FCR and 41.7 months with bendamustine/rituximab (hazard ratio [HR], 1.626; *P* = .001; Figure 4). The trade-off of the enhanced efficacy of FCR was more toxicity, including higher rates of neutropenia (84.2% vs 59.0%; *P* < .001) and infection (39.1% vs 26.8%; *P* = .001).

Overall, the trial confirmed the common belief that FCR provides a longer duration of response but that bendamustine/rituximab is better tolerated, particularly in regard to infections. It is important to keep in mind that the risk of infection is not limited to the 6-month treatment period. Rather, the difference in infection risk was observed in the 6 months after completion of the regimen, suggesting that treatment-related myelosuppression, and perhaps immunosuppression, persists for some time after treatment is completed. Aside from myelosuppression, these regimens are fairly well tolerated.

Newer Antibody-Based Approaches

Several newer CD20-targeting monoclonal antibodies have also demonstrated efficacy in patients with CLL. Obinutuzumab is a humanized glycoengineered antibody that was designed to have greater efficacy than rituximab, with enhanced antibody-dependent cellular cytotoxicity. In an open-label study that enrolled patients with CLL and coexisting conditions, obinutuzumab plus chlorambucil was more effective than rituximab plus chlorambucil as assessed by median PFS (26.7 vs 15.2 months; hazard ratio, 0.39; 95% CI, 0.31-0.49; *P* = .001) and complete response rate (22.3% vs 7.3%; Figure 5).

Toxicities associated with obinutuzumab included infusion-related reactions and neutropenia. Hepatic transaminitis can occur early in the course of treatment, but is usually easily managed by interrupting dosing until symptoms resolve. Obinutuzumab has been approved by the US Food
and Drug Administration (FDA) for use in combination with chlorambucil for the first-line treatment of CLL. The regimen is considered to be fairly well-tolerated and could be an option for older patients or those with comorbidities making them unsuitable for chemoimmunotherapy.

Ofatumumab is a fully humanized anti-CD20 monoclonal antibody. The randomized, open-label, phase 3 COMPLEMENT 1 (Chlorambucil Plus Ofatumumab Versus Chlorambucil Alone in Previously Untreated Patients With Chronic Lymphocytic Leukaemia) trial demonstrated the efficacy and safety of ofatumumab in combination with chlorambucil in patients with previously untreated CLL in whom fludarabine-based chemoimmunotherapy would be challenging based on older age or comorbidities (Figure 6). Ofatumumab is FDA-approved for use in combination with chlorambucil in previously untreated patients with CLL in whom fludarabine-based treatment is not appropriate. However, it is not used as widely as other regimens, perhaps owing to a lack of apparent additional benefit.

Disclosure
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Targeted Agents for the Frontline Management of Chronic Lymphocytic Leukemia

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Early-stage CLL, regardless of disease-specific risk factors, continues to be managed with observation until there is an indication for starting therapy. Early therapeutic intervention has not demonstrated any clinical benefit. Once patients become symptomatic, they proceed to frontline therapy, which may include a variety of approaches depending on the patient’s circumstances. Chemoimmunotherapy continues to be a standard therapeutic approach used for younger, fit CLL patients, particularly those with lower-risk disease features, such as unmutated IGHV genes. However, newer targeted agents have expanded the available treatment options in CLL. The Bruton’s tyrosine kinase (BTK) inhibitor ibrutinib, the phosphoinositide 3-kinase (PI3K)-delta inhibitor idelalisib, and the BCL-2 inhibitor venetoclax are FDA-approved in the relapsed setting (idelalisib is approved in combination with rituximab).

In March 2016, ibrutinib received FDA approval in the frontline setting and is now especially useful for elderly and high-risk patients, providing a valuable alternative to monoclonal antibodies administered alone or with chlorambucil. For patients who develop Richter’s transformation, clinicians must still rely on intensive chemoimmunotherapy regimens and allogeneic stem cell transplant. Frontline trials of idelalisib in combination with other therapies were halted by the FDA in March 2016, based on increased rates of adverse events (AEs), including deaths.

The mechanisms of the newer targeted therapies differ substantially from those of chemotherapy and the CD20-targeted monoclonal antibodies. Both ibrutinib and idelalisib act by interfering with key signaling events that are activated in CLL cells within the microenvironment of secondary lymphoid tissues, such as the lymph nodes and spleen. There, interactions between the leukemia cells and the microenvironment activate the B-cell receptors on the CLL cells, which induces sequential activation of downstream signaling molecules, such as the spleen tyrosine kinase (SYK), Bruton’s tyrosine kinase (BTK), and PI3 kinases, promoting survival and proliferation of CLL cells. Kinase inhibitors have been developed to target and inhibit these specific signaling components within the BCR signaling pathway.

Ibrutinib

Ibrutinib is a covalent inhibitor of BTK, a kinase named after Dr Ogden Bruton, a pediatrician who in the 1950s discovered a primary immunodeficiency syndrome now called Bruton’s agammaglobulinemia or X-linked agammaglobulinemia. In the 1990s, researchers discovered that this syndrome was caused by mutations in a specific kinase, BTK. Pharmaceutical development of BTK-specific inhibitors then commenced. Ibrutinib, the first FDA-approved BTK inhibitor, acts by forming a covalent bond with the cysteine residue (CYS-481) of BTK. Ibrutinib is administered orally once daily and is currently FDA-approved for the treatment of CLL, CLL with 17p deletion, Waldenström macroglobulinemia, and previously treated mantle cell lymphoma.

Ibrutinib is administered orally, which is an important advantage because a large proportion of CLL patients are elderly.

Early evaluation of ibrutinib in CLL demonstrated a remarkable finding: lymph nodes quickly shrink within the first weeks of treatment, concomitant with a transient lymphocytosis in the bloodstream. This event occurs as a result of the redistribution of CLL cells out of the lymphoid tissues and into the peripheral blood, where they are eventually cleared, leading to an objective remission. This redistribution phenomenon is a class effect shared among BTK, SYK, and PI3K inhibitors in CLL, and is caused by inhibition of homing receptor signaling, such as that of chemokine receptors (CXCR4, CXCR5) and adhesion molecules.

The efficacy and safety of ibrutinib in patients with relapsed CLL were evaluated in a phase 1b/2 study. The populations included patients with relapsed or refractory CLL or small lymphocytic leukemia (SLL) who had received a median of 4 prior therapies as well as a small
In this phase 1/2 trial, ibrutinib was associated with an improved PFS when compared with historic data using more traditional salvage options. The median PFS was 28 months in patients with del(17p), and had not been reached at the time of analysis in all other subgroups. Overall, PFS rates remained high in treatment-naive patients and declined somewhat over time in patients with relapsed/refractory CLL, primarily owing to progression in patients with high-risk features and intolerance or complications. However, a majority of patients had durable remissions, even in the relapsed/refractory setting (Figure 7). Similar patterns were noted for overall survival.

Ibrutinib generally is not myelosuppressive, and patients can remain on therapy for an extended time. In anemic and/or thrombocytopenic patients, hemoglobin and platelet levels tend to improve over time, normalizing after 6 to 12 months of ibrutinib in most patients. In the phase 1/2 trial, the most common toxicities were grade 1/2 and required no treatment adjustments or interruptions. These AEs most commonly were diarrhea (49%), upper respiratory tract infections (33%), and fatigue (32%). Patients may experience low-grade musculoskeletal side effects (eg, myalgias or arthralgias), and minor bruising also is relatively common. There were a few cases of severe bleeding possibly related to ibrutinib treatment in patients who were also receiving anticoagulation therapy with warfarin. Therefore, patients taking warfarin were excluded from subsequent clinical trials of ibrutinib.

Infectious complications, which are common in patients with CLL, were also noted during these clinical trials. However, these events were attributed more to the disease than the treatment. Infectious complications tend to develop more frequently during the first year on ibrutinib, when the disease is still present to some extent and patients are not yet in remission. Infections tend to decline in frequency after patients achieve a durable remission.

Many patients from the early studies still continue to receive ibrutinib therapy. An analysis of patients in ibrutinib trials (n=308) evaluated reasons for treatment discontinuation. After a median follow-up of 20 months, the primary reasons for treatment discontinuation were intolerable AEs, complications from the treatment, complications unrelated to the treatment, and disease that progressed as CLL or underwent Richter’s transformation.

Richter’s transformation typically was seen earlier, often within the first year of ibrutinib therapy, with a later plateau in incidence, suggesting that transformed subclones that were already present at the start of ibrutinib treatment progressed and became unmasked during ongoing ibrutinib therapy. In contrast, CLL progression...
with ibrutinib resistance characteristically was seen rather late, after 30 to 36 months on treatment.

The randomized, open-label, phase 3 RESONATE (Study of Ibrutinib Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia) trial compared ibrutinib against ofatumumab in patients with relapsed/refractory CLL or SLL.11 A total of 391 patients were randomly assigned to ibrutinib (420 mg once daily) or intravenous ofatumumab. Patients in the ofatumumab arm could cross over to receive ibrutinib upon disease progression. Ofatumumab, which is FDA-approved in the salvage setting, is associated with a median PFS of approximately 6 to 12 months. After a median follow-up of 9.4 months, ibrutinib was significantly more effective than ofatumumab, with a median PFS not reached in the ibrutinib arm compared with 8.1 months in the ofatumumab arm (HR, 0.22; P<.001). The 12-month OS rate was 90% with ibrutinib and 81% with ofatumumab, and the ORR was 42.6% vs 4.1%, respectively (P<.001).

Based on these clinical studies, ibrutinib received FDA approval for patients with relapsed/refractory CLL. Ibrutinib also received an indication for patients with CLL with del(17p). These patients particularly benefit from ibrutinib because they do not achieve durable responses with conventional chemotherapy.

Subsequently, the randomized, phase 3 HELIOS (Ibrutinib Combined With Bendamustine and Rituximab Compared With Placebo, Bendamustine, and Rituximab for Previously Treated Chronic Lymphocytic Leukaemia or Small Lymphocytic Lymphoma) trial evaluated ibrutinib plus BR vs placebo plus BR in 578 patients with relapsed/refractory CLL or SLL. The trial showed a major efficacy benefit with the ibrutinib-containing regimen.12 After a median follow-up of 17 months, the median PFS was not reached with ibrutinib plus BR, compared with 13.3 months for placebo plus BR (HR, 0.203; 95% CI, 0.150-0.276; P<.0001; Figure 8). The 18-month PFS rates were 79% and 24%, respectively. Minimal residual disease negativity was attained by 9% of patients in the ibrutinib arm vs 2% in the placebo arm, suggesting that ibrutinib may be more likely to induce a deeper remission. Although the trial evaluated the addition of ibrutinib to BR, these findings generated discussion within the CLL community regarding the contribution of BR within this combination. Based on cross-trial comparisons, it does not appear that the PFS associated with ibrutinib plus BR is superior to that attained with single-agent ibrutinib.

The efficacy and safety of ibrutinib in the frontline setting were established in the randomized, open-label, phase 3 RESONATE-2 trial, which compared ibrutinib vs chlorambucil in treatment-naive, older patients with previously untreated CLL or SLL.13 A total of 296 patients ages 65 years or older (median age, 73 years) were randomly assigned to ibrutinib, administered orally at 420 mg daily, or chlorambucil, administered as a pulse every 2 weeks. Patients in the chlorambucil arm who developed progressive disease could receive ibrutinib in an extension study. Chlorambucil-treated patients had higher rates of progression and death.

After a median follow-up of 18.4 months, ibrutinib was significantly more effective than chlorambucil, with the median PFS not reached vs 18.9 months (HR, 0.16; P<.001).13 Estimated 2-year OS rates were 98% and 85%, respectively (HR, 0.16; P=.001). Subgroup analyses identified no significant difference in outcomes based on risk status in the ibrutinib arm, a finding consistent throughout these studies. In contrast, in the chlorambucil arm, higher-risk patients (eg, those with del[11q] or IGHV-unmutated CLL) had worse outcomes than other patients. Finally, the ORR was also significantly higher with ibrutinib vs chlorambucil (86% vs 35%; P<.001). Ibrutinib was also associated with greater sustained improvements in hemoglobin and platelet levels.

The AE profile was similar to that observed in the phase 1/2 study, aside from some added safety signals, including arterial hypertension (reported in 14% of ibrutinib-treated patients), atrial fibrillation (6%), and hemorrhage, reported in 4% of patients receiving ibrutinib vs 2% of patients receiving chlorambucil.13 The incidence of major bleeding events was lower than 5% and did not significantly differ between the arms. Overall, the data from the RESONATE-2 trial indicate that ibrutinib is a valuable option for elderly or high-risk patients who are not candidates for chemoimmunotherapy. Based on these data, ibrutinib received FDA approval in the frontline setting in April 2016.

In summary, ibrutinib is highly effective even for high-risk patients, a group with few options in the past. A key advantage of ibrutinib is its lack of myelosuppression compared with chemoimmunotherapy. It will be interesting to see how second-generation BTK inhibitors, which will likely become available in the next few years, will compete with ibrutinib and other agents in later stages of clinical development.

**Idelalisib**

Idelalisib is a selective inhibitor of PI3 kinase delta that is FDA-approved for the treatment of patients with relapsed CLL in combination with rituximab.3 Preclinical studies have demonstrated that the delta isoform of PI3 kinase plays a key role in B-lymphocyte development. Like ibrutinib, idelalisib is dosed orally. However, whereas ibrutinib is an irreversible covalent inhibitor, idelalisib is a reversible inhibitor and thus requires twice-daily dosing to achieve enzymatic inhibition.

In early-phase clinical trials, idelalisib showed redistribution lymphocytosis that peaked after approximately
8 weeks, with a concomitant reduction in lymph node size of approximately 80% within the first 4 to 6 weeks of treatment. In contrast to ibrutinib, the lymphocytosis associated with idelalisib often resolves more slowly and is sometimes more persistent.

The safety profile of idelalisib differs from that of ibrutinib, particularly in regard to changes in liver function tests, colitis, and pneumonitis. In the phase 1 trial in relapsed/refractory CLL, approximately 20% of patients developed transaminase elevations of any grade; fewer than 5% were higher grade. In the idelalisib combination trials, transaminitis and other autoimmune-type events occurred at a higher rate in patients who were younger or treatment-naive. In addition, there were reports of fatal infectious complications. Therefore, several idelalisib trials were recently placed on hold.

It is possible, however, to avoid the recurrence of transaminitis with dose adjustments. Other AEs associated with idelalisib include fatigue, diarrhea, cough, and back pain. More concerning is the occurrence of late-onset colitis, pneumonia, or pneumonitis, which in some patients are difficult to distinguish, as well as the recently observed infectious complications, which included CMV reactivation, neutropenic fever and sepsis, and pneumocystis infections.

Patients can also develop early diarrhea, which is usually benign and can be managed symptomatically. In the phase 1 trial, 5% to 10% of patients developed late, severe diarrhea. This event could be an on-target effect, as mice lacking PI3 kinase develop autoimmune colitis. Extended administration of idelalisib appears to activate the immune system, including T-cell subsets, and inhibit regulatory T cells, potentially causing autoimmune complications, such as colitis, pneumonitis, liver inflammation, and hepatitis.

To reduce the development of treatment-associated lymphocytosis, idelalisib was evaluated in combination with rituximab. A randomized, double-blind, placebo-controlled, phase 3 study evaluated the combination of idelalisib and rituximab in patients with relapsed CLL with significant comorbidities, who are less able to tolerate standard chemotherapy. Eligible patients had decreased renal function, prior therapy-related myelosuppression, or coexisting illness. A total of 220 patients were randomly assigned to receive rituximab plus idelalisib (150 mg) or placebo twice daily. Patients in the control arm could cross over to idelalisib-based treatment upon progression.

The addition of idelalisib to rituximab was associated with a significant improvement in PFS. The median PFS was not reached in the idelalisib/rituximab arm vs 5.5 months in the rituximab-alone arm (HR, 0.15; P=0.001). The idelalisib arm was also significantly superior to the control arm in regard to ORR (81% vs 13%; odds ratio, 29.92; P=0.001) and 12-month OS rate (92% vs 80%; HR, 0.28; P=0.02). This study, which was enriched for elderly frail patients with
active disease, formed the basis for the FDA approval of idelalisib and rituximab in patients with relapsed CLL.

The incidence of infusion-related reactions was lower with idelalisib plus rituximab vs rituximab alone (15% vs 28%), presumably because the kinase inhibitor affected the immune system. Although the overall rate of AEs was similar between the arms, the idelalisib-containing regimen was associated with higher rates of gastrointestinal AEs, such as diarrhea.17

Idelalisib has also been evaluated in the frontline setting in the treatment of CLL. In 2015, O’Brien and colleagues published results of a phase 2 study evaluating idelalisib plus rituximab in treatment-naive, older patients with CLL.18 The study enrolled 64 patients with a median age of 71 years (range, 65-90 years) who received rituximab plus idelalisib at 150 mg twice daily for 48 weeks. The regimen was associated with an ORR of 97% (19% CRs). Response rates remained high in patients with poor prognostic features. ORR was 100% in those with del(17p)/TP53 mutations and 97% in those with unmutated IGHV.18

The hope from this study was that idelalisib might find a path toward use in previously untreated CLL patients, following the example of ibrutinib. However, as discussed previously, more recent studies showed that idelalisib when used as first-line therapy for CLL was associated with frequent and more severe autoimmune events than observed in previously treated patients, with high rates of grade 3 or higher transaminitis (57%), enterocolitis (14%), and pneumonitis (10%). These higher rates of autoimmune events have been attributed to a more intact T-cell compartment in previously untreated patients.

Based on the increased rates of AEs, including deaths, the FDA released a decision in March 2016 to halt 6 ongoing trials of idelalisib in combination with other therapies in patients with CLL, SLL, and indolent NHL.3 Therefore, at this time, idelalisib in combination with rituximab should be used only in the salvage setting, and patients must be closely monitored. Any autoimmune complications that develop must be managed as appropriate with treatment interruption or the addition of immunosuppressive therapy, such as corticosteroids.

Venetoclax

Venetoclax (ABT-199) is an orally administered inhibitor of BCL-2, an antiapoptotic protein crucial to the survival of CLL cells. It was approved by the FDA in April 2016 for use in CLL patients with the 17p deletion who have been treated with at least 1 previous therapy.1 Development of BCL-2 family inhibitors has been hampered by off-target thrombocytopenia attributed to BCL-XL inhibition.19 As a more selective BCL-2 inhibitor, venetoclax does not negatively affect platelets.

Venetoclax was evaluated in a phase 1/2 study in patients with relapsed or refractory CLL or SLL.20 A total of 56 patients received venetoclax in a dose-escalation phase, and 60 additional patients were treated in an expansion cohort. In the dose-escalation cohort, 3 patients (5%) developed clinical tumor lysis syndrome (TLS), with 1 fatality.20 These developments prompted adjustments to the dose-escalation schedule. The dose was then escalated gradually over a 4-week period up to a maximum of 400 mg per day. No cases of clinical TLS have occurred in the 60 patients receiving the adjusted schedule.

The ORR in the overall treated group was 79%, including 20% CRs. Response rates remained high (71% to 79%) in subgroups with adverse prognostic factors, including fludarabine resistance, del(17p), and unmutated IGHV.20

A potential advantage of venetoclax over kinase inhibitors is its ability to clear all disease compartments, including the bone marrow and the peripheral blood, fairly quickly. Because the phenomenon of lymphocytosis redistribution observed with ibrutinib or idelalisib does not occur with venetoclax, the overall disease burden is cleared more effectively, which may be an advantage in patients who are, for example, being prepared for an allogeneic stem cell transplant. Early data suggest a higher complete response rate with single-agent venetoclax than has been historically observed with kinase inhibitors. This efficacy comes with a price, however, which is the associated risk of tumor lysis syndrome (TLS). Patients receiving venetoclax require hospitalization so they can receive TLS prophylaxis and undergo monitoring for signs of this syndrome if they are considered at intermediate or high risk. Additionally, a significant proportion of patients receiving venetoclax develop neutropenia and associated complications. In the phase 1 trial, 41% of patients developed grade 3/4 neutropenia. Other toxicities included mild diarrhea, reported in 52% of patients, upper respiratory tract infection in 48%, and nausea in 47%.20

The potential advantages and disadvantages of venetoclax must be compared carefully against those of ibrutinib and idelalisib. Because these agents differ in their mechanisms of action, venetoclax may retain activity in patients with CLL refractory to kinase inhibitors. An ongoing, open-label, phase 2 has shown high response rates with venetoclax in patients who develop relapsed or refractory disease after treatment with ibrutinib or idelalisib (Figure 9).21 Therefore, venetoclax could be an effective salvage treatment after ibrutinib and idelalisib, or it could be an effective component of a combination strategy with the goal of obtaining deep remissions and potentially discontinuing treatment.

The concept of a limited treatment period would be an important development in CLL therapy. Current therapies, including ibrutinib and idelalisib, do not induce adequate remissions that would allow patients to discontinue treatment. The hope for the near future is to develop treatment...
approaches that can induce deeper remissions, with no minimal residual disease, allowing patients to remain in remission for an extended period of time.

**Disclosure**

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**References**


Discussion: Managing Risk When Using Idelalisib

Steven E. Coutre, MD, Jan A. Burger, MD, PhD, and John M. Pagel, MD, PhD

**H&O** Could you provide any additional insight into the halting of the first-line trials with idelalisib?

Steven E. Coutre, MD This experience highlighted issues with the drug that we saw early; the longer-term microscopic colitis had already been reported. The recent data reported by Brown and colleagues at the 2015 American Society of Hematology meeting pointed out some issues that might be more prominent in the upfront setting. Data from randomized trials now showing an increased rate of death predominantly related to infectious causes, including those associated with immunosuppression, says that the drug must be used very cautiously. Given its risk-benefit profile and the other options currently available, I think idelalisib moves to a setting for very specific patients with specific needs.

Jan A. Burger, MD, PhD I absolutely agree. In the past, we may have selected patients for one kinase inhibitor or the other based on concerns about certain risks, for example, patients with a high risk for bleeding or recent bleeding. For those patients, we had been more inclined to favor idelalisib, given the ibrutinib-related incidence of bleeding. However, more recent data indicate that in the overall picture, idelalisib has concerning side effects that really favor selection of this drug only for a smaller group of patients.

John M. Pagel, MD, PhD I also concur and suggest that idelalisib should be limited to patients who have failed other lines of therapy. As noted, we have learned that patients who receive idelalisib earlier have done worse than patients who have received it after failing other therapies, which likely represents the degree of immunosuppression, with less-heavily treated patients being more immunocompetent. In particular, idelalisib should not be used in the frontline setting. It is also very important to recognize that idelalisib has a unique side effect profile. Physicians should be aware of its toxicity profile and know how to treat both the commonly observed and the less frequent side effects that may occur.

**Disclosures**

Dr Coutre has received consulting fees from Gilead Sciences and Janssen. He has received funds for research support from AbbVie, Celgene, Gilead Sciences, Janssen, and Pharmacyclics. Dr Burger has received honoraria related to formal advisory activities and as a consultant from Celgene Corporation, Gilead, NOXXON Pharma AG, and Pharmacyclics, Inc. He has received grant support related to research activities from Celgene and Pharmacyclics. Dr Pagel is a consultant for Pharmacyclics and Gilead Pharmaceuticals.

**References**

Diagnosis of CLL

- Most patients diagnosed with CLL are asymptomatic.
- The diagnosis is often made incidentally when routine blood work reveals an elevated white blood cell count or absolute lymphocyte count.
- The diagnosis of CLL requires at least $5 \times 10^9/L$ monoclonal B lymphocytes in peripheral blood, with clonality confirmed by flow cytometry.
- The leukemic cells are small, mature lymphocytes that are typically positive for CD5, CD23, CD19, and CD20.

CLL, chronic lymphocytic leukemia.

Assessing Prognosis in CLL

- Relevant clinical and pathologic factors include:
  - Clinical stage
  - Tumor burden reflected by bulky adenopathy
  - Lymphocyte doubling time
  - Morphologic features, such as the presence of prolymphocytes, which could indicate an evolution from indolent CLL to a more aggressive type
- The patient's age and performance status can also affect prognosis.

Chromosomal Abnormalities in CLL

- Favorable prognosis
  - del(13q)
- Poor prognosis
  - Complex karyotype
  - del(17p)
  - del(11q)
  - TP53 mutations

Initiation of Treatment in CLL

- Early-stage CLL, regardless of disease risk, continues to be managed with observation until there is an indication for starting therapy. Early intervention has not shown a clinical benefit.
- Once patients become symptomatic, they proceed to frontline therapy, which may include a variety of approaches depending on the patient's circumstances.
- Chemoimmunotherapy is still often used for younger, fit patients, particularly those with lower-risk disease.
- Newer targeted agents have expanded the available treatment options in CLL.

Conventional First-Line Treatments

- For older patients and those with significant comorbidities: chlorambucil monotherapy, rituximab monotherapy, or a combination of chlorambucil and rituximab (a regimen used primarily outside the United States).
- For younger patients and those without significant comorbidities: combination chemoimmunotherapy regimens, such as bendamustine/rituximab or fludarabine/cyclophosphamide/rituximab.

Monoclonal Antibodies: Obinutuzumab

- Approved by the FDA for use in combination with chlorambucil for the first-line treatment of CLL.
- In an open-label study that enrolled patients with CLL and coexisting conditions, obinutuzumab plus chlorambucil was more effective than rituximab plus chlorambucil as assessed by median PFS and complete response rate.

**Monoclonal Antibodies: Ofatumumab**

- Approved by the FDA for use in combination with chlorambucil in previously untreated patients with CLL in whom fludarabine-based treatment is not appropriate
- The randomized, open-label, phase 3 COMPLEMENT 1 trial demonstrated the efficacy and safety of ofatumumab in combination with chlorambucil in patients with previously untreated CLL in whom fludarabine-based chemotherapy would be challenging based on older age or comorbidities.
- Not used as widely as other regimens, perhaps owing to a lack of apparent additional benefit.

2. COMPLEMENT Trial: Ofatumumab Versus Chlorambucil Alone Is Preferable to Previously Untreated Patients With Chronic Lymphocytic Leukemia.

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**A New Approval in First-Line Therapy: Ibrutinib**

- In March 2016, ibrutinib received FDA approval in the frontline setting.
- Ibrutinib is especially useful for elderly or high-risk patients, providing a valuable alternative to monoclonal antibodies administered alone or with chlorambucil.
- Early evaluation of ibrutinib in CLL demonstrated that lymph nodes quickly shrink in the first weeks of treatment, concomitant with a transient lymphocytosis in the bloodstream.

FDA, US Food and Drug Administration.

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**Ibrutinib: Clinical Use**

- Ibrutinib is administered orally, which is an important advantage because a large proportion of CLL patients are elderly.
- Ibrutinib is generally not myelosuppressive, and patients can remain on therapy for a longer course.
- Hemoglobin and platelet levels tend to improve over time, normalizing after 6 to 12 months of treatment.

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**Idelalisib in CLL**

- In March 2016, the FDA halted ongoing trials of idelalisib in combination with other therapies in patients with CLL, SLL, and indolent NHL.
- At this time, idelalisib in combination with rituximab should be used only in the salvage setting.
- Patients receiving idelalisib must be closely monitored. Any autoimmune complications that develop must be managed as appropriate with treatment interruption or the addition of immunosuppressive therapy, such as corticosteroids.

NHL, non-Hodgkin lymphoma; SLL, small lymphocytic leukemia.

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