New Pharmacotherapies in Chronic Lymphocytic Leukemia

Jacqueline L. Olin, MS, PharmD, BCPS, CDE, FASHP, FCCP; Katherine Canupp, BS, PharmD Candidate; and Morgan B. Smith, PharmD, BCOP

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western world. The American Cancer Society predicted approximately 18,000 new cases in 2016, with nearly 5,000 estimated deaths. CLL is characterized as a B-cell malignancy, marked by a progressive accumulation of incompetent clonal B lymphocytes with a CLL phenotype. The main diagnostic criterion of CLL is the presence of at least 5 x 10^9 B-cell lymphocytes per liter with a CLL phenotype and by ruling out other lymphoproliferative disorders. In comparison to normal peripheral blood lymphocytes, CLL cells are CD5-positive. In addition, they express B-cell surface antigens CD19, CD20, and CD23. The extent of expression of these surface markers is part of the process involved in distinguishing CLL from other hematologic malignancies.

The exact cause of CLL is unknown, and there are few known risk factors. However, it is more common in men, in people with a family history of the disease, and in people of European genetic ancestry. It is also more common in the elderly, with an average age of 72 years at diagnosis, although up to 30% of cases occur in individuals younger than 55 years of age. Some studies have linked CLL to exposure to chemicals such as Agent Orange. Farming and long-term exposure to some pesticides may potentially increase risk.

Many individuals with CLL are asymptomatic at diagnosis, and the disease may be detected upon routine laboratory examination. Others may present with constitutional symptoms including fever, weight loss, fatigue, night sweats, and weakness, while a physical examination may demonstrate lymphadenopathy, splenomegaly, and hepatomegaly. Depending on prognostic factors and comorbidities, 82.6% of CLL patients are expected to survive at least five years, based on data from the National Institutes of Health’s Surveillance, Epidemiology, and End Results or SEER program. Advances in molecular and cytogenetic analyses have allowed more precise risk-stratification models that have defined current treatment algorithms composed of novel targeted agents. Novel treatment options beyond conventional chemotherapy include monoclonal antibodies and targeted small-molecule inhibitors impacting B-cell signaling. Allogeneic stem cell transplant offers a curative option but is reserved for select individuals: Few qualify given its toxicities. This article describes clinical outcomes and therapeutic application of newly approved pharmacotherapies and highlights emerging investigational therapeutic options.

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PROGNOSTIC FACTORS AND TREATMENT STRATIFICATION

The initial diagnosis of CLL is based on the presence of at least 5 x 10^9 B lymphocytes per liter of peripheral blood with a CLL phenotype and by ruling out other lymphoproliferative disorders. Lymphadenopathy and/or splenomegaly with less than 5 x 10^9 B lymphocytes per liter of peripheral blood is the definition of small lymphocytic lymphoma (SLL), which some experts consider to be a different manifestation of the same disease. Once a diagnosis of CLL is established, the Rai and Binet staging systems are used worldwide in the assessment of prognosis. They are based on physical examination findings and on hemoglobin and platelet concentrations. Both systems define lower-risk disease as the presence of lymphocytosis in the absence of enlarged lymph nodes, splenomegaly, hepatomegaly, anemia, or thrombocytopenia. Individuals with intermediate- and higher-risk CLL have multiple palpable enlarged areas and cytopenias. Median survival times are approximately 12.5 years, seven years, and one to two years for low-, intermediate-, and high-risk CLL, respectively. The Rai and Binet clinical staging systems do not identify which low-risk patients will progress rapidly. Additional molecular markers are used in risk stratification and treatment determination.

Continued progress in understanding the pathology of CLL has led to the discovery of a large number of novel prognostic markers. Establishing a prognostic score for patients with CLL continues to be an area of research, and there are more than 20 such markers available. Immunoglobulin heavy-chain variable (IGHV) mutational status is a strong independent predictor of survival outcomes in CLL, with unmutated (2% or fewer cells mutated) or VH3-21 mutated IGHV indicating a poor prognosis and shorter treatment-free period and overall survival (OS), regardless of stage. Treatment selection is determined by the presence of certain chromosomal abnormalities. In particular, a deletion of chromosomes 11 (del[11q]) and 17 (del[17p]) and/or mutation of the TP53 gene have been associated with worse prognosis. Therefore, evaluation for the presence of these three specific cytogenetic abnormalities, among others, has been incorporated into treatment guidelines, particularly before each anticipated treatment to account for mutations occurring over the course of the disease. Treatment options are stratified by cytogenetic abnormality (Table 1).

TREATMENT PRINCIPLES

With the exception of allogeneic hematopoietic stem cell transplantation (HSCT), CLL is not generally considered curable. However, long-term disease-free survival has been demonstrated in some subsets of patients. Goals of chemo-
therapy include inducing remission and prolonging life while minimizing treatment-related adverse effects. No survival advantage was demonstrated when comparing immediate with deferred initiation of treatment in older trials of alkylating agents. Therefore, chemotherapy is not offered in earlier stages where presentation is often asymptomatic; patients are managed with periodic follow-up until the development of signs and symptoms, including progressive lymphadenopathies, splenomegaly, or cytopenias. The current availability of more targeted therapies and molecular markers points to the need for continued research into the impact of earlier treatment options.

Historically, chlorambucil (Leukeran, Aspen Global) was the standard therapy for initial treatment, and it is still an option today, most often given in combination with an anti-CD20 monoclonal antibody. A phase 3 trial comparing fludarabine to chlorambucil in patients with a median age of 70 years showed improved complete response (CR) with fludarabine, but no difference in OS. Thus, chlorambucil monotherapy remains a first-line option for older patients with comorbidities. Introduction of the biologic agent rituximab, an anti-CD20 monoclonal antibody, revolutionized the management of B-cell malignancies, including CLL, with the combination of fludarabine, cyclophosphamide, and rituximab (FCR) becoming the recognized gold standard in patients able to tolerate intensive therapy.

In the CLL8 trial, untreated physically fit patients were randomized to receive six courses of FCR or fludarabine and cyclophosphamide (FC). Progression-free survival (PFS) was higher in the FCR group after three years (65% versus 45%; hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.46–0.69). With 5.9 years of follow-up, median OS was 86 months for the FC group and not yet reached for the FCR group (P = 0.001). However, patients with del(17p) did not benefit as much from FCR, and older patients with comorbidities, including reduced renal function, may not tolerate FCR as well as other options. Data from a phase 2 FCR study showed that patients with a mutated IGHV gene achieved sustained remission after a median 12.8 years of follow-up, which was the first success of this type demonstrated in CLL. The combination of bendamustine with rituximab (BR) was compared with FCR in untreated physically fit patients and did not meet the prespecified criteria for noninferiority. Because BR was associated with fewer infectious complications, it remains a consideration for older patients at risk for infections.

Front-line chemotherapy options for CLL are stratified based on del(17p)/TP53 mutations and the patient’s fitness level or ability to handle intensive chemotherapy (Table 1).

### BIOLOGIC THERAPIES

#### Anti-CD20 Antibody Therapies

Because the addition of rituximab to fludarabine and cyclophosphamide demonstrated improved activity and was well tolerated, FCR became a first-line therapy. Further research into the biological activity of the CD20 receptor led to the development of ofatumumab (Arzerra, Novartis) and obinutuzumab (Gazyva, Genentech), which have distinct CD20-binding characteristics. Ofatumumab, a fully human monoclonal CD20 antibody, and rituximab have been classified as type-1 anti-CD20 antibodies because they lead to binding with C1q, which activates complement-dependent cytotoxicity (CDC). However, ofatumumab binds at distinct, discontinuous regions of CD20, which differentiates it from rituximab. Obinutuzumab, a type-2 anti-CD20 antibody, binds to CD20 with less intensity, resulting in lower CDC but more lysosomal cell death (antibody-dependent cellular cytotoxicity). Continued studies of ofatumumab and obinutuzumab will help further define the clinical impact of their molecular differences.

### New Pharmacotherapies in Chronic Lymphocytic Leukemia

#### Table 1 Selected First-Line Treatment Options for Chronic Lymphocytic Leukemia

<table>
<thead>
<tr>
<th>CLL Without del(17p) and/or TP53 Mutation</th>
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<tbody>
<tr>
<td><strong>Physically Fit Patients</strong></td>
</tr>
<tr>
<td>• Fludarabine + cyclophosphamide + rituximab</td>
</tr>
<tr>
<td>• Pentostatin + cyclophosphamide + rituximab</td>
</tr>
<tr>
<td>• Fludarabine + rituximab</td>
</tr>
<tr>
<td>• Bendamustine + rituximab</td>
</tr>
<tr>
<td><strong>Elderly or Frail Patients or Those With Significant Comorbidities</strong></td>
</tr>
<tr>
<td>• Obinutuzumab + chlorambucil&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Ibrutinib&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Ofatumumab + chlorambucil</td>
</tr>
<tr>
<td>• Rituximab + chlorambucil</td>
</tr>
<tr>
<td>• Bendamustine + rituximab&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>• Idelalisib + rituximab&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>• High-dose methylprednisolone + rituximab</td>
</tr>
<tr>
<td>• Allogeneic stem cell transplant</td>
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</tbody>
</table>

**CLL** = chronic lymphocytic leukemia; del(17p) = chromosome 17 deletion; NCCN = National Comprehensive Cancer Network.  
<sup>a</sup> Category 1 recommendation as per NCCN guidelines  
<sup>b</sup> Not guideline-recommended for patients categorized as frail  
<sup>c</sup> Not endorsed by NCCN
### Table 2 New Pharmacotherapies in Chronic Lymphocytic Leukemia

<table>
<thead>
<tr>
<th>Medication (Brand, Manufacturer)</th>
<th>Drug Class</th>
<th>Indication Recommended Dose</th>
<th>Adverse Effects*</th>
<th>Additional Comments</th>
<th>Cost24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biological Therapies: CD20 Antagonists</strong></td>
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</tr>
</tbody>
</table>
| Obinutuzumab (Gazyva, Genentech)19 | Humanized IgG1 monoclonal antibody | Untreated CLL in combination with chlorambucil:  
*Cycle 1 (28 days)*  
Day 1 – 100 mg IV  
Day 2 – 900 mg IV  
Day 8 – 1,000 mg IV  
Day 15 – 1,000 mg IV  
Cycles 2–6  
Day 1 – 1,000 mg IV every 28 days  
Premedicate with acetaminophen, corticosteroid, and antihistamine 30–60 minutes prior to infusion. | • Infusion reactions  
• Neutropenia  
• Thrombocytopenia  
• Anemia  
• Pyrexia  
• Cough  
• Nausea  
• Diarrhea | • Screen for HBV prior to initiation and monitor during treatment and for several months after discontinuation.  
• Use cautiously or discontinue if HBV reactivation occurs during treatment.  
• Patients with pre-existing cardio-pulmonary conditions are at increased risk for severe infusion reactions.  
• Live virus vaccines are not recommended during treatment.  
• There is potential for progressive multifocal leukoencephalopathy. | Strength: 25 mg/1 mL  
Package size: 40 mL  
AWP per mL = $167.93 |
| Ofatumumab (Arzerra, Novartis)20 | Fully human IgG1-kappa monoclonal antibody | Untreated CLL or relapsed CLL in combination with fludarabine and cyclophosphamide:  
*Cycle 1 (28 days)*  
Day 1 – 300 mg IV  
Day 8 – 1,000 mg IV  
Cycles 2–12  
Day 1 – 1,000 mg IV in every subsequent 28-day cycle (maximum 12 cycles for treatment naïve or 6 cycles for relapsed disease)  
**Extended treatment in patients who responded to at least two lines of therapy:**  
**Cycle 1:** Same as above.  
Then 1,000 mg 7 weeks later and every 8 weeks up to a maximum of 2 years.  
For all indications, premedicate with acetaminophen, corticosteroid, and antihistamine 30–120 minutes prior to infusion | • Infusion reactions  
• Neutropenia | | Strength: 20 mg/1 mL  
Package size: 50 mL  
AWP per mL = $124.91 |

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the CLL11 trial.19,28 Given the age and comorbidities present in the majority of individuals with CLL, the CLL11 trial evaluated participants with coexisting conditions. Treatment-naïve patients with comorbidities (N = 781), as indicated by either a cumulative illness rating scale score greater than 6 or moderate renal impairment, were randomized to one of three arms: chlorambucil alone, obinutuzumab plus chlorambucil, or rituximab plus chlorambucil. Patients’ median age was 73 years, and 82% had at least three comorbidities. Median PFS was significantly improved in both combination arms (26.7 months, 16.3 months, and 11.1 months in the obinutuzumab plus chlorambucil, rituximab plus chlorambucil, and chlorambucil groups, respectively; HR for progression or death, 0.18; 95% CI, 0.13–0.24; P < 0.001 for obinutuzumab plus chlorambucil compared with chlorambucil). Direct comparison of obinutuzumab plus chlorambucil with rituximab plus chlorambucil demonstrated prolonged PFS (HR, 0.39; 95% CI, 0.31–0.49; P < 0.001.) The PFS benefit with obinutuzumab did not extend to those patients with del(17p).28 Grade 3 or 4 infusion reactions occurred in 20% of participants during the first obinutuzumab
Table 2  New Pharmacotherapies in Chronic Lymphocytic Leukemia (continued)

<table>
<thead>
<tr>
<th>Medication (Brand, Manufacturer)</th>
<th>Drug Class</th>
<th>Indication</th>
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<th>Adverse Effects*</th>
<th>Additional Comments</th>
<th>Cost24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib (Imbruvica, Pharmacyclics)21</td>
<td>Bruton’s tyrosine kinase inhibitor</td>
<td>Untreated or relapsed/refractory CLL: 420 mg orally once daily until disease progression or unacceptable toxicity</td>
<td>Neutropenia, Thrombocytopenia, Diarrhea, Anemia, Musculoskeletal pain, Rash, Nausea, Bruising, Fatigue, Hemorrhage, Pyrexia</td>
<td>Avoid use with moderate or strong CYP3A inducers and inhibitors (including grapefruit products, Seville oranges, starfruit). Avoid use in patients with moderate or severe hepatic impairment. Monitor CBC monthly during treatment, including differential. Fetal risk has been demonstrated. Patients ≥ 65 years old have increased risk for serious adverse effects.</td>
<td>Strength: 140 mg Package size: 90 or 120 capsules AWP per capsule = $136.57</td>
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</tr>
<tr>
<td>Idelalisib (Zydelig, Gilead)22</td>
<td>PI3K-delta inhibitor</td>
<td>Relapsed/refractory CLL, in combination with rituximab: 150 mg orally twice daily until disease progression or unacceptable toxicity</td>
<td>Diarrhea, Pyrexia, Fatigue, Nausea, Cough, Pneumonia, Abdominal pain, Chills, Rash, Neutropenia, Hypertriglyceridemia, Hyperglycemia, ALT/AST elevations</td>
<td>Avoid CYP3A inducers and substrates. Serious allergic reactions, including anaphylaxis, have been reported. May cause fetal harm when administered during pregnancy.</td>
<td>Strengths: 100 mg or 150 mg Package size: 60 tablets AWP per tablet = $191.14</td>
<td></td>
</tr>
<tr>
<td>Venetoclax (Venclexta, AbbVie)23</td>
<td>BCL-2 inhibitor</td>
<td>Relapsed/refractory CLL, with 17p chromosome deletion: Titrate from 20 mg orally once daily to 400 mg orally once daily over five weeks. Premedicate with IV fluids, xanthine oxidase inhibitor, or urate oxidase inhibitor as clinically indicated</td>
<td>Neutropenia, Diarrhea, Nausea, Anemia, Upper respiratory tract infection, Thrombocytopenia, Fatigue</td>
<td>Avoid live attenuated vaccines prior to, during, and after therapy until B-cell recovery occurs. Avoid use with moderate or strong CYP3A inducers and inhibitors (including grapefruit products, Seville oranges, starfruit) and P-glycoprotein inhibitors. May cause fetal harm when administered during pregnancy.</td>
<td>Strengths: 10 mg, 50 mg, 100 mg Package sizes: 2 or 14 tablets (10 mg), 1 or 7 tablets (50 mg), 1 or 120 tablets (100 mg) AWP per tablet = $9.56 (10 mg), $47.80 (50 mg), $95.60 (100 mg)</td>
<td></td>
</tr>
</tbody>
</table>

* Common adverse effects seen in 10% or more patients with ofatumumab or obinutuzumab; common adverse effects seen in 20% or more patients with other agents.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AWP = average wholesale price; BCL-2 = B-cell lymphoma-2 protein; CBC = complete blood count; CLL = chronic lymphocytic leukemia; CYP = cytochrome P450; HBV = hepatitis B virus; IgG1 = immunoglobulin G1; IV = intravenously; PI3K = phosphatidylinositol-3 kinase.

infusion and were more severe with obinutuzumab, but not during subsequent infusions.25

Obinutuzumab demonstrated activity in heavily pretreated patients in a phase 1/2 study, but it is not approved by the FDA for this indication.29 Patients administered obinutuzumab should receive acetaminophen, a corticosteroid, and an antihistamine 30–120 minutes prior to infusion and should be closely monitored during the infusion for blood pressure changes, flushing, pyrexia, chills, and other infusion reactions.19
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Ofatumumab

Ofatumumab plus chlorambucil was evaluated in the COMPLEMENT-1 trial, a phase 3 study in treatment-naïve CLL patients deemed to be ineligible for fludarabine based on age or comorbidities.\textsuperscript{39,40} Participants were randomized to receive ofatumumab with chlorambucil (n = 221) or chlorambucil alone (n = 226) with continued treatment until best response or a maximum of 12 cycles, with the primary endpoint of median PFS. Participants’ median age was 69 years, and 72% had at least two comorbidities, which included cardiovascular, metabolic, respiratory, renal, or other conditions. After 28.9 months of follow-up, PFS was improved in the combination therapy arm with median PFS of 22.4 months versus 13.1 months (HR, 0.57; 95% CI, 0.45–0.72; \(P = 0.001\)). In patients with del(17p), PFS was unchanged with the addition of ofatumumab (HR, 0.46; 95% CI, 0.18–1.19). Patients receiving combination therapy were more likely to experience neutropenia, but rates of infection were similar between groups. Grade 3 and 4 infusion reactions were experienced in 10% of patients. As with obinutuzumab, patients receiving ofatumumab should receive premedication and should be closely monitored for infusion reactions. The findings of this trial led to FDA approval of ofatumumab with chlorambucil in untreated patients ineligible for fludarabine.\textsuperscript{29,30}

Ofatumumab is also FDA-approved with fludarabine and cyclophosphamide for relapsed disease, as extended treatment in patients who responded to at least two lines of therapy, and for patients failing fludarabine or alemtuzumab.\textsuperscript{33} Its activity in the setting of relapsed disease was demonstrated in the COMPLEMENT-2 study with improved PFS of ofatumumab with FC compared with FC alone (HR, 0.67; 95% CI, 0.51–0.88; \(P = 0.0032\)).\textsuperscript{31} The PROLONG investigators evaluated ofatumumab as a maintenance therapy in 238 patients for up to two years compared with observation, and improved PFS was observed with therapy (HR, 0.50; 95% CI, 0.38–0.66; \(P < 0.001\)).\textsuperscript{32} Activity of ofatumumab has been observed in patients failing fludarabine or alemtuzumab.\textsuperscript{29,33}

Small-Molecule Therapies

Ibrutinib

Ibrutinib is a small-molecule therapy and Bruton’s tyrosine kinase (BTK) inhibitor approved for several hematologic malignancies.\textsuperscript{21} BTK has a well-characterized role in the B-cell receptor signaling pathway that leads to proliferation and cell survival.\textsuperscript{34,35} Specifically, it promotes homing and adhesion of CLL cells to the microenvironment, an activity that is chemokine-mediated.\textsuperscript{36,37} Ibrutinib forms covalent bonds with a cysteine residue in the active site of the BTK.\textsuperscript{21} This leads to an inhibition of enzymatic activity of the BTK and thus inhibits malignant B-cell proliferation and survival, resulting in cell death.\textsuperscript{21}

Ibrutinib was compared with chlorambucil in an international, open-label, randomized phase 3 trial of 269 previously untreated patients with CLL at least 65 years of age.\textsuperscript{32} Up to half of the participants had creatinine clearance of less than 60 mL/min at baseline, and a third had a cumulative illness rating score greater than 6. Treatment with ibrutinib resulted in longer rates of PFS and OS. The relative risk of progression or death was 84% lower with ibrutinib (HR, 0.16; 95% CI, 0.09–0.28; \(P = 0.001\)).\textsuperscript{31} Adverse effects of ibrutinib included grade 3–4 major hemorrhages in five patients. Grade 2–3 atrial fibrillation occurred in six patients with drug discontinuation in two patients, and grade 3 hypertension occurred in six patients, none requiring dose modification. In a follow-up analysis of this trial and other studies of ibrutinib in previously treated patients, median PFS and OS still hadn’t been reached, with more than 89% PFS at two years.\textsuperscript{30} Outcomes were favorable with ibrutinib in previously treated patients as well.\textsuperscript{30} Patients taking ibrutinib should be educated about and monitored for signs and symptoms of bleeding, infection, and atrial fibrillation.\textsuperscript{21}

Idelalisib

Idelalisib is another small molecule that affects B-cell signaling pathways. Phosphatidylinositol-3 kinases (PI3Ks) in lymphocytes and other cells regulate processes such as proliferation and migration and have been shown to be expressed in isolated B-CLL cells.\textsuperscript{30,41} Inhibition of the PI3K-delta isoform pathway leads to enhanced apoptosis.\textsuperscript{41} Idelalisib is an inhibitor of PI3K-delta that affects signaling through B-cell receptor pathways by inducing apoptosis.\textsuperscript{25} It is approved in combination with rituximab for treatment of relapsed or refractory CLL based on findings of the Study 116 trial.\textsuperscript{22,42} The combination of idelalisib and rituximab was compared with rituximab alone in CLL patients who had progressed on previous regimens with a median of at least three drugs; PFS was the primary endpoint. Patients (N = 220) had a median age of 71 years with median estimated creatinine clearance of 62–67 mL per minute. Median PFS was 5.5 months in the rituximab-only arm and had not yet been reached with combination therapy when the study was halted at the prespecified stopping point for efficacy (\(P = 0.001\)). OS at one year was improved with combination therapy (92% versus 80%; HR, 0.28; \(P = 0.02\)). Of note, the PFS benefit of idelalisib was extended to those patients with del(17p).\textsuperscript{42} Given the activity of idelalisib and the limited options for patients with del(17p), idelalisib was approved in Europe for treatment-naïve patients with del(17p) and is recommended by the German CLL study group as an option for first-line therapy in this subgroup.\textsuperscript{4}

Of concern with idelalisib are fatal or severe hepatotoxicity, severe diarrhea or colitis, and serious or fatal infections, which occurred in 18%, 14%, and 21% of patients in monotherapy trials and 11%, 19%, and 36% of patients in combination trials, respectively.\textsuperscript{22} In a phase 2 study of idelalisib as first-line therapy, 54% experienced grade 3 or higher transaminitis.\textsuperscript{22} A safety analysis was conducted with patients receiving idelalisib for multiple indications. Of 1,073 evaluated patients, 51% experienced transaminitis of any grade with median onset of 39 days. Rechallenge of some participants with at least grade 3 transaminitis resulted in no further recurrence.\textsuperscript{44} Patient counseling for idelalisib should include monitoring and awareness to alert the provider about severe skin reactions, diarrhea, or new or worsening coughing or shortness of breath.\textsuperscript{22}

Venetoclax

While improved CLL outcomes have been demonstrated with ibrutinib and idelalisib, there is still the potential for relapse and resistance, particularly in patients with del(17p). The B-cell lymphoma-2 (BCL-2) family of proteins regulates cellular apoptosis and oncogenic functions. Selective inhibi-
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tion of BCL-2 has resulted in tumor lysis within 24 hours.\textsuperscript{45} Venetoclax (Venclexa, AbbVie/Genentech) is thought to bind BCL-2 and restore apoptosis.\textsuperscript{22} This small-molecule therapy is approved specifically for patients with del(17p) CLL who have received at least one prior therapy.\textsuperscript{23}

Venetoclax was studied in a phase 1 dose-escalation study (150–1,200 mg per day) of 116 participants with relapsed or refractory CLL or SLL.\textsuperscript{23,58} Patients’ median age was 66 years, they had received from one to 11 previous therapies, and 30% had the del(17p) mutation. The overall response rate (ORR) across all doses was 79%, with a 71% response rate among those with del(17p). Clinically significant tumor lysis syndrome (TLS) occurred in three patients, with one requiring dialysis and one sudden death after a dose increase. In the study expansion with revised dose-escalation adjustments and administration of TLS prophylactic medications in higher-risk participants, no clinically significant TLS occurred. Other adverse effects included diarrhea (52%), upper respiratory infection (48%), and grade 3–4 neutropenia (41%).\textsuperscript{46} At 24 months, the subset of participants maintained on the 400-mg daily dose had estimated PFS of 62% (95% CI, 45–75%). Grade 3 or higher adverse events occurred in 86%, with neutropenia as the most common. Most were treated with granulocyte-colony stimulating factor, and all responded.\textsuperscript{47}

A phase 2 study of 107 participants with relapsed or refractory CLL demonstrated 79.4% ORR (95% CI, 70.5–86.6) at one year. Some participants had failed ibrutinib or idelalisib, which provides further support for venetoclax in higher-risk populations.\textsuperscript{48} Several studies are under way evaluating venetoclax in previously untreated CLL, including various combinations with ibrutinib, obinutuzumab, and rituximab (NCT02758665, NCT02756897, and NCT02950051).\textsuperscript{49–51}

Patients receiving venetoclax should be instructed to drink at least six glasses of water daily, should be educated about symptoms of TLS, and should receive appropriate TLS prophylaxis as indicated. Inpatient dose initiation and escalation is recommended for high-risk patients, such as those with any lymph nodes 10 cm or larger or with an absolute lymphocyte count of 25 x 10\textsuperscript{9} per liter or greater and any lymph nodes 5 cm or larger.\textsuperscript{23}

HSCT

Prior to the availability of the small-molecule therapies, allogeneic HSCT was the only treatment option for relapsed/refractory high-risk patients, such as those with del(17p). Use of RIC regimens has expanded accessibility and produced curative potential, but GVHD has been a limitation. While small-molecule therapies provide alternatives for managing high-risk patients, their long-term efficacy remains unknown. HSCT may still be a viable option for some patients. A suggested sequencing of modalities is the use of the novel agents until, ideally, an achievement of a maximum response (or even if no response) and then HSCT, especially in younger patients with a well-matched donor available.\textsuperscript{52}

EMERGING THERAPIES

Acalabrutinib (ACP-196)

BTK inhibition has become an important advance in the treatment of CLL because this target has been shown to be highly active in the malignancy.\textsuperscript{34–36} However, ibrutinib is associated with high levels of toxicity, drug resistance due to incomplete BTK receptor blockade, and Richter’s transformation (evolution of CLL into large-cell lymphoma).\textsuperscript{53,54} Acalabrutinib (ACP-196, Acerta Pharma) is a second-generation irreversible inhibitor of BTK that offers several pharmacological improvements compared with its first-generation counterpart. This agent represents a more selectively targeted BTK inhibitor that does not bind to alternative kinases, such as epidermal growth factor receptor, TEC family, and insulin receptor kinase, thereby providing improved tolerability. In addition, acalabrutinib has more rapid oral absorption (peak plasma values occur between 0.6 and 1.1 hours versus one and two hours) and a shorter half-life (one hour versus four to 13 hours) compared with ibrutinib, allowing for twice-daily dosing. This method of administration has been shown to provide better plasma exposure (continuous, greater-than-95% blockade of BTK) than ibrutinib. As a result, rates of drug resistance and Richter’s transformation may be effectively reduced.\textsuperscript{55}

Acalabrutinib was initially shown to be safe and effective in an uncontrolled, multicenter, phase 1/2 trial of 60 relapsed/refractory CLL patients in which the ORR with 100-mg twice-daily dosing was 95% (partial response [PR], 85%; PR with lymphocytosis, 10%) with a median follow-up period of 14.3 months. Stable disease (SD) occurred in 5% of patients. ORR in patients with del(17p) was 100%. No cases of Richter’s transformation were reported, and only a single case of disease progression occurred. Patients had a median of three prior therapies, and a majority had poor prognostic features. Most toxicities were grade 1–2, with the most common being headache (43%), diarrhea (39%), increased weight (26%), pyrexia (23%), and upper respiratory infection (23%). Therapy discontinuation due to toxicity occurred in three patients (3%).\textsuperscript{55} Preliminary findings in an ongoing phase 1/2 study (NCT02029443) of acalabrutinib in 74 patients with treatment-naive CLL reflected similar results (ORR, 96%; PR, 86%; PR plus lymphocytosis, 10%; SD, 4%). The median time to response was two months, with a rapid reduction in lymphadenopathy. Treatment was highly tolerable, with 97% of patients continuing on the study drug.\textsuperscript{56} A phase 3 trial is under way based on these results (NCT02475681).\textsuperscript{57}

Lenalidomide

Lenalidomide (Revlimid, Celgene), an FDA-approved immunomodulatory agent for multiple myeloma, mantle cell lymphoma, and myelodysplastic syndrome,\textsuperscript{58} is being explored as a treatment option for CLL. Although well known for its antiangiogenic, antineoplastic mechanisms, lenalidomide is classified as an immunomodulatory agent due to its ability to enhance the immune system. It counters T-cell dysfunction known to exist in patients with CLL and also inhibits the suppressive effects that malignant CLL clones have on the immune system.\textsuperscript{59–61} Among the mechanisms of cancer-induced immune-system suppression discovered to date, checkpoint inhibition has been identified as a potential target in CLL. Malignancies of many types, including CLL, use the programmed death receptor-1 (PD-1) pathway to diminish the growth and activity of T cells that would normally be malignant cell lysis.\textsuperscript{62,63} Lenalidomide blocks the inhibitory interaction that occurs between the programmed death receptor ligand-1 (PD-L1)
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found on malignant cells and the PD-1 found on CD4+ and CD8+ T cells, thereby increasing T-cell cytotoxicity and enhancing immune system function.60

Existing data suggest a potential role for lenalidomide in the management of CLL. Trials to date have demonstrated an ORR of 56% and 58% when lenalidomide is given as monotherapy at 10–25 mg orally daily on days 1–21 of a 28-day schedule in both the untreated and relapsed/refractory settings.64,65 Toxicities unusual to lenalidomide but found in studies with CLL patients include TLS and a unique “tumor flare.” This flare has been positively correlated with response rates in clinical trials and is characterized by symptoms associated with immune-system activation, specifically increased B-cell antigen presentation. These symptoms include acute lymphadenopathy with inflammation in the overlying skin, fever, and rash.66 Titrating CLL patients from lower doses (5–10 mg daily) by 5 mg every 28 days to 25 mg daily may provide noninferior response rates and reduce the incidence of the flare reaction.66

Although combinations of lenalidomide with traditional chemotherapy agents were found to be prohibitively toxic, lenalidomide has been combined with anti-CD20 monoclonal antibodies to provide synergy and added efficacy without excessive toxicities.67,68 Addition of rituximab to lenalidomide is associated with ORR approaching 83% in the first-line setting and 61% in the relapsed/refractory setting, with or without the presence of poor prognostic features.69,70 Lenalidomide has been included in the National Comprehensive Cancer Network guidelines as a treatment option both alone and in combination with rituximab in the relapsed/refractory setting, regardless of mutation status.4 However, it is still not recommended in the first-line setting, nor has the FDA granted approval for lenalidomide use in CLL. The combination of lenalidomide and the second-generation anti-CD20 monoclonal ofatumumab may provide even better results, with phase 2 data suggesting an ORR of 71% with 24% CR in the relapsed/refractory setting.71 Further studies with anti-CD20 monoclonal antibodies are in development and should help elucidate the role of lenalidomide in CLL.

**CAR T-Cell Therapy**

Antineoplastic treatment strategies that harness the immune system have become the mainstay of cancer research today. In particular, therapies meant to amplify T cells in the adaptive immune system have become the mainstay of cancer research today. Other Agents

Outside of the emerging therapies previously discussed, many other pharmacotherapeutic mechanisms are being researched for the management of CLL. Phase 2 studies are under way for novel antibodies targeting the B-cell lineage-specific CD37 (NCT02538614) and CD19 (NCT01466153, NCT02005289) surface antigens.77–79 In addition, checkpoint inhibitors, specifically those that target PD-1 and PD-L1, are being researched as part of combination regimens in both the untreated and relapsed/refractory settings. However, given the dysfunctional T-cell state found in CLL, the malignancy is relatively resistant to PD-1 inhibition alone, and development of the agents as monotherapy is unlikely to occur.79,80 Preclinical data suggest PD-1 inhibitors act in a synergistic manner with BTK inhibitors,80 and a phase 2 study of combination therapy with nivolumab (Opdivo, Bristol-Myers Squibb) and ibrutinib is ongoing in patients with relapsed/refractory or high-risk untreated CLL (NCT02420912).81
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ECONOMIC CONSIDERATIONS

Given that CLL is the most common leukemia in the United States and primarily affects older individuals, most treatment costs are borne by Medicare. Average wholesale prices per unit of the newer treatments appear in Table 2. The economic burden for CLL has to be considered in the context that patients may require multiple lines of therapy and possibly HSCT. The cost of ibrutinib at standard dose could be expected to be higher than $100,000 per year, which can exceed the cost of some HSCT scenarios. A systematic review of the literature identifying costs in CLL reported annual direct costs per person of $43,913 in the United States, with 26.2% to 79% potentially attributable to drug therapy. In comparison, the median 100-day total cost for an allogeneic SCT was estimated at $203,026. However, if patients receive multiple lines of drug therapy, the potential estimated costs are in the millions of dollars. While intravenous therapies are covered by Medicare Part B, the newer oral agents will be covered by Medicare Part D, which will shift more cost burden to patients. The shift of cost responsibility to the patient may impact adherence, which may in turn, affect the degree of response to therapy.

CONCLUSION

New therapeutic advances have changed the treatment landscape for patients with CLL. New biological therapies, including ofatumumab and obinutuzumab, and small-molecule inhibitors, including ibrutinib, idelalisib, and venetoclax, provide innovative mechanisms in both the first-line and relapsed/refractory treatment settings. Some of these therapies have demonstrated activity against highly resistant, harder-to-treat CLL and offer alternatives or additions to HSCT. Key emerging therapies, including strategies that target the immune system, have shown some great potential. The cost of treatment, especially when multiple lines may be needed, will greatly influence management and must be considered in treatment decisions, both from an individual patient and a societal perspective.

REFERENCES


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