

Evolving Approaches to the Treatment of Chronic Lymphocytic Leukemia With Targeted Therapies

DESPITE THE WIDE RANGE of survival duration in patients with chronic lymphocytic leukemia (CLL), the median overall survival (OS) for patients with CLL is roughly 10 years from diagnosis.¹ Approximately one-third of patients with CLL never require treatment for their disease and will die from causes other than CLL. Other patients will develop disease-related symptoms that do require treatment, and for them, therapeutic advances in oncological care have resulted in greater control of disease for substantial periods of time. As the treatment spectrum expands, a new emphasis on managing CLL as a chronic disease—ie, gaining control of symptoms, preventing progression, avoiding secondary diseases, and reducing issues that decrease quality of life—has emerged.^{2,3}

Although many patients with CLL have indolent disease and are managed initially with a “watch and wait” approach, most eventually develop active disease and require treatment.^{1,4,5} Novel advancements in CLL therapy are needed to maintain long survival rates and combat the eventual development of relapsed or refractory (R/R) disease and medication intolerance. Many patients with CLL who undergo therapy will eventually relapse or progress, resulting in the need for multiple lines of therapy that include combinations of medications. In addition, patients may experience intolerance to specific regimens or develop cumulative toxicities requiring different therapy.

Recently, several new targeted therapies that facilitate the management of CLL as a chronic disease were developed. This article will review the new classes and practical considerations of their use.

Treatment Options

Before targeted therapies, the mainstay of treatment for younger patients with CLL in otherwise good health was combination therapy; specifically, the combination of fludarabine, cyclophosphamide, and rituximab or the combination of bendamustine and rituximab. The goal of these high-intensity regimens was durable remission, with negative minimal residual disease (MRD) at the end of treatment. However, these regimens are not appropriate for elderly patients or those with significant comorbidities.⁵ Moreover, CLL is rarely observed in individuals aged <40 years; the median age at diagnosis is between 67 and 72 years.^{1,6} At diagnosis, >70% of patients are 65 years or older.¹ For these patients with CLL who require treatment, low-intensity regimens, such as chlorambucil plus

an anti-B-lymphocyte antigen CD20 antibody (eg, rituximab), are preferred in the majority. The goal of therapy is to prevent CLL-related symptoms, ameliorate anemia, and improve thrombocytopenia.⁵

Novel targeted agents (eg, duvelisib, ibrutinib, acalabrutinib, idelalisib, and venetoclax), as well as new anti-CD20 antibodies (eg, ofatumumab and obinutuzumab), have provided additional treatment options for elderly patients and those with significant comorbidities or high-risk markers such as del(17p) or *TP53* mutation.^{4,7-14} In addition to offering manageable safety profiles and convenient oral options, targeted agents may advance the life expectancy of patients with CLL. One study compared the OS of patients with CLL to the life expectancy of 72-year-old individuals without CLL.¹⁵ Patients with CLL were treated with either single-agent chlorambucil or single-agent ibrutinib. After 3 years, approximately 75% of patients in the chlorambucil group were still alive, compared with an estimated 97% of patients in the ibrutinib group. These results suggest that treatment with ibrutinib may allow for a normal life expectancy in elderly patients with CLL.¹⁵

Updated results from a phase 3 study that evaluated the addition of an anti-CD20 antibody (either obinutuzumab or rituximab) to chlorambucil in elderly patients with coexisting conditions demonstrated longer OS in patients treated with the combination compared with those treated with chlorambucil monotherapy. These results suggest that combination therapy can prolong the life of elderly patients with CLL.^{14,16}

New Agents in CLL

Bruton Tyrosine Kinase Inhibitors

Ibrutinib is currently the only Bruton tyrosine kinase (BTK) inhibitor approved for use in patients with CLL and small lymphocytic leukemia (SLL) during initial treatment or through relapse. BTK is a signaling molecule involved in the activation of pathways that are necessary for B-cell trafficking, chemotaxis, and adhesion.¹⁷ Many patients with CLL respond to ibrutinib monotherapy regardless of the line of therapy.^{7,8,18,19} Even patients with high-risk genetic characteristics, such as del(17p) or del(11q), have experienced clinically meaningful progression-free survival (PFS) and OS improvements.^{18,20} The recommended dosing in CLL is 420 mg orally once daily. The most common ($\geq 20\%$) adverse events (AEs) in patients with B-cell malignancies are neutropenia, thrombocytopenia, diarrhea, anemia,

musculoskeletal pain, rash, nausea, bruising, fatigue, hemorrhage, and pyrexia.¹⁷

Acalabrutinib is a second-generation oral BTK inhibitor that is currently under investigation for the treatment of CLL and SLL.²¹ A phase 1/2 study demonstrated a partial response (PR) rate of 85% in patients with relapsed CLL; an additional 8% to 10% of patients achieved PRs with lymphocytosis. In this study, patients received doses ranging from 100 to 400 mg orally daily; patients in the expansion phase received 100 mg twice a day or 200 mg once a day. The most common AEs ($\geq 20\%$) included headache, diarrhea, upper respiratory tract infection, fatigue, nausea, arthralgia, pyrexia, contusion, petechiae, increased weight, peripheral edema, and hypertension.^{22,23} Additionally, patients with an intolerance to ibrutinib were found to be successfully transitioned to acalabrutinib.²⁴ Because acalabrutinib binds to the same site as ibrutinib, acalabrutinib has no activity against CLL cells with *BTK*C481S mutations and should not be given to ibrutinib-resistant patients with this mutation.^{4,22} Additional trials in patients with CLL are currently under way.²⁵⁻²⁷

PI3K Inhibitors

Idelalisib is a phosphoinositide 3-kinase (PI3K) inhibitor specific to the δ -isoform. It inhibits several signaling pathways that affect the trafficking and homing of B cells to lymph nodes and bone marrow. It is currently FDA approved for use in relapsed SLL in patients who have had at least 2 prior systemic therapies and for use in patients with relapsed CLL in combination with rituximab.²⁸ In a phase 3 trial that compared rituximab monotherapy against idelalisib in combination with rituximab, patients with heavily pretreated CLL experienced a significantly higher overall response rate (ORR) when treated with the combination versus monotherapy (ORR, 81% vs 13%, respectively; $P < .001$). All responses were partial.⁹ The recommended starting dose of idelalisib is 150 mg twice daily orally, and the most common AEs ($\geq 20\%$) included diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, pneumonia, and rash.¹⁷

Duvelisib is the most recently approved PI3K inhibitor. Duvelisib demonstrates dual inhibitory activity against PI3K- δ and PI3K- γ isoforms, offering another distinct treatment option for patients with R/R CLL and SLL.²⁹ In a follicular lymphoma xenograft model, significantly greater inhibition of tumor growth with the dual PI3K- δ and PI3K- γ inhibitor duvelisib was observed compared with PI3K- δ or PI3K- γ selective inhibitors, although this increase in activity has not been confirmed in clinical trials.³⁰ In the phase 3 DUO study, patients with at least 1 prior therapy who received duvelisib experienced an improvement in median PFS compared with patients who received ofatumumab

(median PFS, 16.4 months vs 9.1 months; HR, 0.4). The ORR was 78% in the duvelisib group and 39% in the ofatumumab group (difference in ORR, 39%). All responses were PRs.^{11,29} The duvelisib dose is 25 mg taken orally twice a day, and the most common AEs ($\geq 20\%$) included diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anemia.²⁹

Duvelisib has also shown clinical and pharmacodynamic activity in expansion cohorts in patients with R/R CLL and patients with treatment-naïve CLL. In a phase 1 study, duvelisib was administered twice daily in 28-day cycles in varying doses; mean ORRs were 56.4%, with a median response duration of 21 months in patients with R/R disease.³¹ Mean ORRs were 83.3% in treatment-naïve patients. Based on these results, duvelisib was selected for further investigation in a phase 3 study in R/R CLL.³¹

Duvelisib has also recently been shown to exhibit synergistic interactions when used in combination with a variety of other agents.³² Conducting a high-throughput combination screen in malignant lymphoid cell lines with a variety of standard-of-care and experimental agents important in lymphoma therapy, investigators found significant combination activity with agents such as dexamethasone, ibrutinib, and venetoclax.³² These findings indicate that duvelisib, when combined with such other agents as BTK inhibitors and B-cell lymphoma 2 (BCL-2) antagonists, may represent an effective strategy for inhibiting tumor growth in patients with CLL.

BCL2 Antagonists

Venetoclax, the first agent of BCL-2 inhibitor class approved by the FDA, is a highly selective, small molecule inhibitor of BCL-2 that is approved for use as a second-line therapy in patients with CLL and SLL with or without del(17p). BCL-2 is an antiapoptotic protein that has been found to be overexpressed in CLL cells, where it mediates tumor cell survival and may be associated with resistance to chemotherapy.³³ In a phase 1 dose-escalation trial in patients with R/R CLL and SLL, tumor lysis syndrome was observed in 3 of 56 patients, which resulted in adjustments to the dose escalation schedule. After the changes in dosing, there were no reports of clinical tumor lysis syndrome in any of the 60 patients in the expansion group. There was a 79% ORR among all 116 patients who received venetoclax, with 20% of these patients experiencing complete remission. Patients in high-risk groups also demonstrated response rates ranging from 71% to 79%. High-risk groups included patients with del(17p), del(11q), and unmutated *IGHV*, and those who had been heavily pretreated (>4 prior lines of therapy).¹⁰ Another phase 2 study also demonstrated an ORR of 79.4% in patients with R/R CLL with del(17p).³⁴

The results of a phase 3 study of patients with R/R CLL

illustrated that the 2-year rate of PFS was 84.9% among patients receiving venetoclax in combination with rituximab, compared with 36.3% in patients receiving bendamustine plus rituximab. The PFS advantage was also seen across several high-risk groups, including patients with del(17p), mutated *TP53*, and unmutated *IGHV*. In the overall population, the ORR with venetoclax plus rituximab was found to be 92.3%, with complete responses observed in 8.2% of patients. Clearance of MRD was 62.4% in patients who received venetoclax plus rituximab.³⁵

The current recommendations regarding venetoclax include a ramp-up dosing schedule in which patients begin with 20-mg oral doses once daily for 7 days; doses increase weekly until the recommended daily dose of 400 mg is reached. The most common AEs ($\geq 20\%$) include neutropenia, diarrhea, nausea, upper respiratory tract infection, anemia, fatigue, thrombocytopenia, musculoskeletal pain, edema, and cough.³³

Anti-CD20 Antibodies

Ofatumumab is a fully humanized anti-CD20 antibody that differs from rituximab in its binding site.³⁶ Ofatumumab has been shown to be active as a monotherapy in patients with CLL who were refractory to fludarabine and alemtuzumab, and it is currently approved for the use as monotherapy in this setting.^{13,37} However, ofatumumab monotherapy has been found to have inferior response rates in patients with R/R CLL when compared with ibrutinib and duvelisib in head-to-head studies.^{11,18} The COMPLEMENT 1 study included treatment-naïve patients with CLL who were unable to tolerate a fludarabine-based regimen. In the study, treatment with ofatumumab plus chlorambucil resulted in a median PFS of 22.4 months compared with 13.1 months in patients treated with chlorambucil alone ($P < .0001$).¹² Ofatumumab is given as an intravenous infusion with indication-specific dosing schedules. The most common AEs reported in $\geq 10\%$ of patients for any CLL indication include infusion reactions, neutropenia, leukopenia, febrile neutropenia, upper respiratory tract infection, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infection.³⁷

Another anti-CD20 antibody, obinutuzumab, is a glycoengineered antibody.³⁸ In a phase 1/2 study that included patients with R/R CLL, those treated with obinutuzumab monotherapy had an ORR of 62% in the phase 1 segment and 15% in the phase 2 segment.³⁹ A phase 3 study evaluated chlorambucil plus an anti-CD20 antibody (either rituximab or obinutuzumab) in patients with CLL. Treatment with chlorambucil plus obinutuzumab resulted in prolonged median PFS (26.7 months) when compared with chlorambucil

monotherapy (11.1 months) and chlorambucil plus rituximab (16.3 months; $P < .001$ for both).¹⁴ Obinutuzumab is currently approved for use in combination with chlorambucil for patients with treatment-naïve CLL. In this population, the most common AEs include infusion reactions, neutropenia, thrombocytopenia, and diarrhea.³⁸

Practical Considerations

Elderly Patients

The development of new therapies for the treatment of CLL has encouraged an individualized approach to treatment that will be based on patient-specific risk factors.⁵ Because elderly patients can differ dramatically in physical health and comorbidities, the availability of varying treatment options that can be customized for patient-related and disease-related risk factors is important.⁴⁰ Decreased level of hematopoietic reserve is an important factor to consider when treating older patients with CLL. It can put them at a high risk of myelotoxicity.⁴¹ When looking at safety data from studies specific to elderly patients, neutropenia grade 3 or higher occurred in 33% to 35% of patients who received chlorambucil plus obinutuzumab (CLL11), 26% of patients who received chlorambucil plus ofatumumab (COMPLEMENT 1), and 10% of patients who received ibrutinib (RESONATE II).^{7,12,14} Although ibrutinib appears to be associated with a low incidence of neutropenia, 2 other ibrutinib-associated AEs should be considered in elderly patients: fatal hemorrhage and atrial fibrillation.^{17,42} Elderly patients are at high risk for atrial fibrillation, and the use of anticoagulants for thrombosis prevention in atrial fibrillation is complicated further by the risk of hemorrhage associated with ibrutinib.^{42,43}

High-Risk Groups

Several biological markers have been associated with poor clinical outcome in CLL, including del(17p), del(11q), unmutated *IGHV* genes, and *TP53* mutations.¹ Many newer agents have shown improved efficacy in difficult-to-manage groups of patients. The majority of these newer agents have demonstrated efficacy in patients with del(17p); however, ibrutinib demonstrates efficacy in the first-line setting and in patients with R/R disease.^{44,45} Ibrutinib plus venetoclax, as well as rituximab, idelalisib, rituximab, and duvelisib, has shown efficacy in patients with mutated *TP53* genes.^{11,34,44-48} Patients with unmutated *IGHV* have experienced clinical benefit from idelalisib and rituximab.⁴⁸

Resistance to Prior Therapy

Consideration should be given to the development of acquired resistance to certain agents. In particular, recent evidence suggests that resistance to ibrutinib is associated with mutations in *BTK* and in phospholipase *Cy2* genes.^{49,50} In an interim analysis of a phase 2 study, venetoclax

demonstrated an ORR of 65% among patients who were resistant to prior therapy with ibrutinib.⁵¹ Further studies regarding the efficacy of agents in the setting of BTK inhibitor resistance are warranted.

Patient Convenience

Many of the new kinase inhibitors indicated for use in CLL are oral therapies that can be self-administered at home. However, some agents (eg, venetoclax and idelalisib) are often recommended for use in combination with anti-CD20 antibodies. They are intravenous infusions that require healthcare facility visits.⁴ Oral agents that are recommended and approved for use as a monotherapy in CLL include ibrutinib and duvelisib.^{4,17,29}

Consideration should also be given to the complexity of the self-administered oral agents. Venetoclax has a ramp-up schedule to minimize the incidence of tumor lysis syndrome, which can potentially be difficult for patients to execute properly. To facilitate the ramp-up schedule, venetoclax is available as 10-mg, 50-mg, and 100-mg tablets. The recommended final dose is 400 mg daily, requiring 4 tablets per dose, making pill burden another potential concern.³³

Conclusions

Recent advances in the treatment landscape for CLL have brought forth many new options. In particular, new agents have provided more effective options with manageable safety profiles for elderly patients or those with significant comorbidities who cannot tolerate conventional chemoimmunotherapy. Patients with certain biological markers have also gained several new options that are effective in high-risk populations. In addition, many new therapies are orally self-administered, providing simpler and potentially more convenient options for patients. Guidance regarding the sequencing of these options would be invaluable, especially when acquired resistance is observed. Further studies regarding effective options in the setting of acquired resistance are needed.

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