Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is characterized by the accumulation of abnormal lymphocytes in the blood, bone marrow, and lymphoid tissues, leading to a weakened immune system and an increased risk of infections for patients. The NCCN Guidelines for CLL/SLL underscore the need for a comprehensive evaluation of multiple factors to determine the most appropriate treatment approach for each patient. For frontline therapy, the selection process should consider the patient’s IGHV status, del(17p)/TP53 mutation status, age, and comorbidities. In choosing subsequent therapy, prior therapy, comorbidities, and resistance mutations should be considered. With no clear evidence of a functional cure, it is important to enroll patients in clinical trials when available.

**Frontline Therapies**

In terms of frontline therapies, Dr. Stephens outlined the preferred treatment options as recommended in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CLL/SLL:

- Acalabrutinib (a Bruton’s tyrosine kinase [BTK] inhibitor) ± obinutuzumab (an anti-CD20 monoclonal antibody)
- Venetoclax (BCL2 inhibitor) + obinutuzumab
- Zanubrutinib (a BTK inhibitor)$^1$

These options are recommended across almost every subgroup of patients, said Dr. Stephens. “The treatment algorithm begins with assessing the availability of relevant clinical trials, because enrolling patients in these trials remains crucial for advancing treatment and finding a cure for CLL and SLL,” she said. “In the absence of suitable clinical trials, the algorithm considers IGHV status and fluorescence in situ hybridization results to determine the most appropriate treatment approach.”

For patients with mutated IGHV and deletion 13q alone who are aged ≤70 years, fludarabine/cyclophosphamide/rituximab (FCR) therapy may be considered. However, Dr. Stephens emphasized, this regimen is not preferred in the current era of targeted therapies for CLL and SLL.

In cases of unmutated IGHV and 17p deletion or TP53, patients should be directed toward second-generation BTK inhibitors. For other patients, the choice of treatment depends on their comorbidities and specific circumstances.

When choosing between venetoclax + obinutuzumab and BTK inhibitors (Figure 1), Dr. Stephens underscored the importance of considering the following factors:

- Uncontrolled atrial fibrillation or hypertension (favoring venetoclax)
- Need for anticoagulation (favoring venetoclax)
- Patient preference for time-limited therapy (venetoclax + obinutuzumab is given for 12 months, whereas BTK inhibitors are given continually)
- Renal insufficiency (favoring BTK inhibitors)
- Extensive infections (favoring BTK inhibitors, except in cases of aspergillosis)

The GAIA/CLL13 study, conducted by the German CLL group, enrolled 920 fit, treatment-naïve patients with...
CLL, excluding those with a 17p deletion. The investigators compared various treatment options, including chemoinmunotherapy (FCR or BR [bendamustine + rituximab]), venetoclax + rituximab, venetoclax + obinutuzumab, and a triplet combination of obinutuzumab, venetoclax, and ibrutinib. Results showed that most patients achieved undetectable measurable residual disease (MRD) status with the latter 2 treatment options, with obinutuzumab proving more effective than rituximab. The 3-drug combination had similar undetectable MRD results as the obinutuzumab + venetoclax arm.

“With a follow-up of about 39 months, the GAIA (CLL13) study indicates that the obinutuzumab + venetoclax arm and the 3-drug regimen arm have improved progression-free survival [PFS] for treatment-naïve patients with CLL over chemoimmunotherapy and rituximab + venetoclax,” said Dr. Stephens. “However, it is unclear whether the addition of ibrutinib to venetoclax and obinutuzumab will provide significant benefits over time, and longer follow-up is needed.”

The Alliance A041702 study, which focused on older patients with CLL (aged ≥65 years), compared ibrutinib + obinutuzumab with the 3-drug combination of ibrutinib + venetoclax + obinutuzumab. An interim analysis revealed no PFS benefit for the 3-drug arm, leading to the discontinuation of patient enrollment and treatment on that arm.

The ongoing CLL17 study aims to determine the best combination of highly effective and minimally toxic drugs to benefit patients with CLL. The study compares continuous ibrutinib therapy, venetoclax + obinutuzumab, and ibrutinib + venetoclax combined. Dr. Stephens noted several pros and cons. Among the pros, the lead-in eliminates the risk of high tumor lysis, thereby avoiding hospitalization for venetoclax ramp-up. This combination also allows for time-limited use of BTK inhibitors, which are effective in the frontline setting. Additionally, responses to ibrutinib have been observed following relapse after this regimen, suggesting that time-limited therapy may limit the number of patients who become resistant to the drug.

Among the cons, however, Dr. Stephens noted the toxicity observed in patients aged >65 years, including hypertension, atrial fibrillation, and bleeding. “It is unclear whether this toxicity would be reduced with second-generation BTK inhibitors such as acalabrutinib or zanubrutinib, but ongoing studies may provide answers,” said Dr. Stephens.

When considering subsequent treatment, Dr. Stephens recommended assessing the availability of clinical trials, reviewing treatment history, considering comorbidities, monitoring creatinine clearance, and determining TP53 mutation status, and evaluating BTK resistance mutations for patients with prior BTK inhibitor treatment (Figure 2). For patients who have received both BTK inhibitors and venetoclax, clinical trials are strongly recommended.

Dr. Stephens also mentioned the phase III MURANO trial, which paired venetoclax with rituximab in the second-line setting. This drug combination resulted in significantly longer PFS than BR. Obinutuzumab is considered a preferable antibody over rituximab for patients with CLL, said Dr. Stephens, but its use in the second-line setting is not yet supported by phase III data.

For patients who received venetoclax + obinutuzumab in the frontline setting, Dr. Stephens suggested 2 main options: switching to the BTK inhibitor class or, if the patient has been in remission for >12 months, potentially re-treating with venetoclax + obinutuzumab.
The 12-month cutoff is based on the available data, but it is not a hard and fast rule, said Dr. Stephens. In cases where patients had prior BTK inhibitor treatment, it is advised to check for BTK resistance mutations using next-generation sequencing. If no resistance mutations are present, alternative BTK inhibitors, such as acalabrutinib or zanubrutinib, can be used because they have been shown to have improved tolerance compared with ibrutinib. If a resistance mutation is detected, venetoclax-based therapy would be the preferred choice.

**Retreatment With Venetoclax**

In a recently published study, 46 patients with CLL were retreated with venetoclax and results demonstrated reasonable response rates, according to Dr. Stephens. However, the overall response rate for re-treatment was lower than with initial treatment, with 33.3% of patients achieving complete response and 46.2% achieving partial response. Median PFS from the end of the first venetoclax treatment to starting the second was approximately 2 years, said Dr. Stephens, who noted more data are needed to determine the most appropriate patient population for venetoclax re-treatment.

**ELEVATE-RR and ALPINE Trials**

Dr. Stephens discussed 2 significant trials focused on BTK inhibitors, specifically comparing the second-generation and first-generation BTK inhibitors.

The ELEVATE-RR study was designed for patients with relapsed/refractory CLL, specifically targeting a higher-risk population with 17p and 11q deletions. After 41 months of follow-up, the PFS curves for both acalabrutinib and ibrutinib were found to be almost equivalent, demonstrating noninferiority. However, during the period between 12 and 27 months, the acalabrutinib curve appeared to have a benefit over ibrutinib before eventually overlapping at around 3 years.

Of note, the study also revealed that acalabrutinib resulted in lower toxicity rates compared with ibrutinib. Cumulative rates of atrial fibrillation, hypertension, bleeding, diarrhea, and arthralgia were all lower with acalabrutinib.

Although the ELEVATE-RR study targeted a higher-risk population, the ALPINE study, which compared ibrutinib and zanubrutinib, included all-comers with relapsed/refractory CLL, encompassing various risk factors. At 15 months, zanubrutinib led to a 78% overall response rate compared with 63% for ibrutinib. Furthermore, the study demonstrated that zanubrutinib was superior to ibrutinib in terms of PFS: at 24 months, 80% of patients receiving zanubrutinib were still progression-free compared with 67% of those receiving ibrutinib.

Zanubrutinib also was associated with significantly lower rates of toxicity, particularly atrial fibrillation. Conversely, the rate of hypertension was similar to ibrutinib. On the other hand, there were numerically fewer major bleeding events and events leading to treatment discontinuation with zanubrutinib. One notable side effect of zanubrutinib was a tendency to cause more neutropenia, although this did not correlate to neutropenic fever or higher rates of grade 3 infections.
“The findings of these 2 studies have led to a shift toward using second-generation BTK inhibitors due to their comparable efficacy and reduced toxicity,” said Dr. Stephens.

Choosing Between BTK Inhibitors

According to Dr. Stephens, acalabrutinib is considered the most well-tolerated regimen with the fewest side effects, making it suitable for older patients and those with uncontrolled hypertension. Zanubrutinib, on the other hand, offers an option for once-daily dosing, making it a potential choice for patients who may struggle with compliance with twice-daily dosing. The PFS benefit observed in the ALPINE study also supports its recommendation for many patients.

For ibrutinib, ongoing studies with ibrutinib + venetoclax may lead to insurance approval for ibrutinib alone. Patients already on ibrutinib therapy may choose to continue, said Dr. Stephens, because they may experience side effects such as headaches when switching to acalabrutinib or other commonly seen side effects during the first few months of treatment.

“Future research and long-term follow-up will be crucial in further understanding the advantages and limitations of these second-generation BTK inhibitors, ultimately helping to determine the most effective treatment strategies for patients with CLL,” said Dr. Stephens.

Pirtobrutinib

Pirtobrutinib, formerly known as Loxo 305, is a novel oral, noncovalent, and selective BTK inhibitor that does not require binding at C481. It is being studied as a potential treatment for patients who develop resistance to covalent BTK inhibitors, which most commonly occurs after 2 to 3 years of therapy.

The BRUIN study, a large phase I/II trial, has reported on 261 heavily pretreated patients with CLL treated with pirtobrutinib, showing an overall response rate of almost 70%. PFS was found to be independent of BTK mutation status. In January 2023, pirtobrutinib was approved for relapsed/refractory mantle cell lymphoma, making it available on the market for this indication, although it is still under review for use in CLL.

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References