CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

Active Treatment in High-Risk, Early-Stage CLL or SLL

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H&O How often do patients present with asymptomatic, early-stage chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), and how many of these patients experience progression to advanced disease?

DS Patients who have CLL or SLL present with asymptomatic, early-stage disease approximately 70% of the time. Approximately 50% of the patients who are asymptomatic at diagnosis will experience progression to advanced disease.

H&O What factors define *high risk* in early-stage CLL or SLL?

DS One nice tool used to determine risk is the CLL International Prognostic Index (CLL-IPI) score, which combines elements of clinical risk factors and molecular or laboratory-based test findings. The clinical risk factors identified with this score are age older than 65 years and Rai stage I to IV, each of which adds 1 point to the risk score. The laboratory-based risk factors include unmutated *IGHV* status and elevated beta$_2$-microglobulin level (>3.5 mg/L), each of which adds 2 points to the score, and the presence of del(17p) and/or *TP53* mutations, each worth 4 points on the scale if either is present. Once the points are added, the score indicates the risk level. *Low risk* is indicated by 0 to 1 points, *intermediate risk* by 2 to 3 points, *high risk* by 4 to 6 points, and *very high risk* by 7 or more points. Although this scale originally was used to predict overall survival (OS), it is now best used to estimate time until first CLL-directed treatment. Patients at higher risk have a shorter time to first treatment. OS is not quite as predictable as it once was because the ongoing development of newer and better drugs is prolonging OS.

H&O What is the current standard of care for asymptomatic patients with high-risk disease, and what are its limitations?

DS The current standard of care for asymptomatic patients with high-risk disease is observation, with clinical and laboratory monitoring for symptoms and cytopenias (anemia or low platelet count) that would require CLL-directed therapy. Symptoms that may indicate the need for therapy include pain associated with enlargement of the lymph nodes or spleen, fevers or drenching night sweats in the absence of active infection, unplanned weight loss (≥10% of body weight over a 6-month period), and significant fatigue interfering with daily activities.

One limitation of this approach is that patients must become sicker before treatment is administered. The CLL burden is typically greater at the time treatment is started, and patients with a greater disease burden may be at elevated risk for side effects like tumor lysis syndrome. Another limitation is that we still have no cure for CLL.

H&O What is the rationale behind the EVOLVE CLL/SLL study, and why venetoclax and obinutuzumab specifically?

DS The rationale behind EVOLVE CLL/SLL is that although older, nonspecific chemotherapy treatments like fludarabine did not improve OS, novel agents causing deep remissions with fewer side effects—such as venetoclax (Venclexta, AbbVie/Genentech) and obinutuzumab (Gazyva, Genentech)—had not been studied as early

intervention (NCT04269902).

Venetoclax and obinutuzumab were chosen because this combination is a highly effective and preferred option for the frontline treatment of CLL. Side effects are limited but include tumor lysis syndrome, which is more likely in patients with a greater disease burden. Also, unlike drugs such as Bruton tyrosine kinase (BTK) inhibitors, which are used as continuous therapy, the regimen of venetoclax and obinutuzumab is time-limited, with treatment required for only 12 months. Less treatment over time generally reduces side effects and cost. Therefore, we have hypothesized that patients treated with early venetoclax and obinutuzumab will have fewer side effects and a better quality of life, will be more likely to achieve deep and prolonged remissions, and will survive longer than patients who receive delayed venetoclax and obinutuzumab.

> The side effects of venetoclax plus obinutuzumab are expected to be the same whether treatment is early or delayed.

H&O Which patients are eligible for EVOLVE?

DS Adult patients who have received a diagnosis of CLL or SLL within the last 18 months, have a CLL IPI score of at least 4 and/or a complex karyotype, are asymptomatic, and do not meet any of the criteria for initiating CLL-directed therapy are potentially eligible to participate in EVOLVE.

H&O Can you walk us through the study design?

DS Patients are randomized in a 2:1 ratio to either early venetoclax and obinutuzumab or delayed venetoclax and obinutuzumab.

The treatment regimen is given over a total of 12 months. For the first 6 months, patients will receive periodic intravenous infusions of obinutuzumab plus daily oral venetoclax pills. For the second 6 months, patients will receive only daily oral venetoclax pills.

The primary endpoint is OS. Our goal is to compare the survival times of the patients in the 2 arms. We hypothesize that early treatment will lead to a longer OS.

Secondary endpoints include progression-free survival, response rates, safety, time to next CLL-directed treatment, rate of Richter transformation, ability to achieve undetectable residual disease, and improvements in quality of life.

H&O What are the potential risks or concerns regarding the initiation of venetoclax and obinutuzumab before patients meet the standard treatment criteria?

DS The side effects of venetoclax plus obinutuzumab are expected to be the same whether treatment is early or delayed. The most common side effect of obinutuzumab is an infusion-related reaction, which is usually quickly reversed by stopping the infusion and giving medications to reverse the response. The most notable side effect of venetoclax is tumor lysis syndrome, which occurs when cancer cells die quickly and waste products from inside the cells—such as potassium, uric acid, and phosphorus—are released into the bloodstream. Tumor lysis syndrome can overwhelm the kidneys or lead to cardiac arrhythmias. The risk of tumor lysis syndrome is quite low overall because the obinutuzumab is started 3 weeks before the venetoclax, and the dose of venetoclax is ramped up slowly over 5 weeks. Venetoclax can also cause mild nausea and a drop in the neutrophil or platelet count, which can lead to infection or bleeding. One disadvantage of early treatment is that the side effects occur earlier. An additional risk is that some patients on observation might never have needed treatment, so it is possible for them to be exposed to unneeded treatments. We selected patients at high risk for the trial, however; symptoms will develop in nearly all these patients, and they will need CLL-directed treatment.

H&O What did CLL12 teach us about early ibrutinib (Imbruvica, Pharmacyclics/Janssen) in this setting, and why might the venetoclax-based approach in EVOLVE tell a different story?

DS The phase 3 CLL12 study was a well-designed trial that randomized asymptomatic patients with CLL to either continuous ibrutinib or continuous placebo.[1] Although the study did show a benefit of early ibrutinib in terms of progression-free survival, it did not show a benefit in terms of OS. Notably, almost as many side effects were observed in the placebo arm as in the ibrutinib arm, which tells us that just living with untreated CLL creates its own set of side effects that adversely affect quality of life. This study did not result in a change in the standard of care because early ibrutinib did not prolong OS.

This study has been criticized because it is now known that ibrutinib causes more side effects and carries a greater

overall risk than some of the newer BTK inhibitors, such as acalabrutinib (Calquence, AstraZeneca) and zanubrutinib (Brukinsa, BeiGene). It is unknown whether use of a drug with fewer side effects may have led to different outcomes. An additional criticism is that the drug is given continuously. This means that the amount of drug (and exposure to its cost and side effects) is increased over a person's lifetime if the drug is started early.

H&O What other ongoing early intervention trials are you watching closely?

DS PreVent-ACaLL is a phase 2 study that randomizes patients to 3 months of acalabrutinib plus venetoclax or standard observation (NCT03868722). The goal of the trial is to reduce the CLL burden and restore the immune system, which we hope will reduce the rates of infections and other CLL-related complications over time.

H&O Do you believe that measurable residual disease (MRD) could become a meaningful endpoint—or even a treatment-guiding tool—in the setting of early intervention?

DS MRD might become a meaningful endpoint in the setting of early intervention, although it would depend on which treatment is used. The clinical benefit of continuous single-agent BTK inhibitors is not based on the achievement of undetectable MRD, so MRD is not as useful in this setting. Also, multiple ways to assess MRD are available, most commonly flow cytometry and next-generation sequencing, but at this time the field does not agree on the best method, and the sensitivity of each test for detecting residual disease is slightly different. MRD testing can be slow and/or technically challenging, so it is not available at all centers. Overall, we need a more standardized and more accurate approach to assessing MRD before it can become a meaningful standard endpoint.

H&O If EVOLVE demonstrates an OS benefit, how will that reshape guidelines and clinical practice for high-risk, early-stage CLL?

DS If EVOLVE demonstrates an OS benefit, it will change the standard of care and reshape the guidelines to recommend early treatment with venetoclax and obinutuzumab for patients with high-risk CLL.

Disclosures

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Reference

1. Langerbeins P, Zhang C, Robrecht S, et al. The CLL12 trial: ibrutinib vs placebo in treatment-naïve, early-stage chronic lymphocytic leukemia. *Blood*. 2022;139(2):177-187.