

Improving Outcomes for Patients With Chronic Lymphocytic Leukemia

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Mazyar Shadman, MD, MPH, and Amy Goodrich, CRNP, reviewed data regarding the mechanistic activity, efficacy, and safety of approved and emerging therapeutic options for chronic lymphocytic leukemia (CLL) and strategies for managing adverse events associated with approved therapies for CLL.

With over 20,000 new cases and nearly 4,000 deaths anticipated in 2020, chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world, accounting for approximately 30% of leukemias (American Cancer Society, 2020). At JADPRO Live 2019, Mazyar Shadman, MD, MPH, Fred Hutchinson Cancer Research Center and the University of Washington, and Amy Goodrich, CRNP, Johns Hopkins School of Medicine and Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, evaluated data regarding approved and emerging therapeutic options for CLL and discussed strategies for managing treatment-related adverse events.

As Ms. Goodrich, a research associate and nurse practitioner, explained, CLL is typically a disease of the elderly but can also occur in younger patients. Because nearly 60% of patients are asymp-

tomatic, however, diagnosis can be a challenge. A diagnostic work-up is essential, said Ms. Goodrich, and should include the following: peripheral blood flow cytometry, physical exam, performance status, B symptoms, complete blood count with differential/platelets, comprehensive metabolic panel, lactate dehydrogenase, hepatitis B screen, and bone marrow biopsy and aspirate (Table 1).

Dr. Shadman, an assistant professor of medical oncology, noted that all patients who meet 2018 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria should be offered therapy. Prior to starting therapy for CLL, however, both fluorescence in situ hybridization (FISH) and next-generation sequencing (NGS) panels should be performed.

"*TP53* is one of the most important prognostic and predictive biomarkers and should be determined prior to therapy," said Dr. Shadman, who noted that some patients will have *TP53*

Table 1. Updated 2018 International Workshop on CLL (iwCLL) Guidelines to Initiate Therapy**Any one of the following criteria should be met to initiate CLL therapy:**

- Progressive marrow failure, hemoglobin < 10 g/dL or platelet count of < 100 × 10⁹/L
- Massive (≥ 6 cm below the left costal margin) or progressive or symptomatic splenomegaly
- Massive (≥ 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
- Autoimmune complications of CLL that are poorly responsive to corticosteroids
- Symptomatic extranodal involvement (e.g., skin, kidney, lung, spine)
- Disease-related symptoms, including
 - » Unintentional weight loss of ≥ 10% within the previous 6 months
 - » Significant fatigue
 - » Fever ≥ 100.5°F for 2 or more weeks without evidence of infection
 - » Night sweats for ≥ 1 month without evidence of infection

Note. Information from Hallek et al. (2018).

on NGS but no del(17p) on FISH. “*IGVH* mutational status can also inform treatment decisions.”

One of the main reasons for FISH and molecular testing, Dr. Shadman added, is that the presence of p53 mutation or deletion should exclude patients from receiving chemotherapy. Dr. Shadman also emphasized that the treatment of CLL is usually postponed until iwCLL guidelines are met. That is, early treatment with either ibrutinib or chemotherapy has not demonstrated an improvement in overall survival.

SUGGESTED REGIMENS FOR FRONT-LINE TREATMENT OF CLL

Regardless of del(17p) or *TP53* mutation status, ibrutinib, acalabrutinib (approved since the presentation), or venetoclax and obinutuzumab are options in the first-line setting, said Dr. Shadman, but ibrutinib has more robust data in terms of long-term activity. However, there are advantages and disadvantages to the three regimens.

According to Dr. Shadman, venetoclax and obinutuzumab is attractive because it offers potentially a time-limited treatment. Venetoclax is given for 1 year of treatment and obinutuzumab for 6 months before stopping. Despite the fixed duration of treatment, the venetoclax combination demonstrated a progression-free survival benefit over chemotherapy, and after finishing 1 year of treatment, 75% of patients tested negative for minimal residual disease (MRD) in the bone marrow (intention-to-treat population). Although longer follow-up is needed to show an overall survival advantage, said Dr. Shadman, that level of MRD eradication is not

seen with ibrutinib or the second-generation BTK inhibitor, acalabrutinib.

With ibrutinib, on the other hand, treatment is continued until resistance or toxicity. Because ibrutinib has been around the longest, however, there is solid long-term follow-up data. Recently published data from the RESONATE-2 study showed 5-year follow-up in the first-line setting on ibrutinib along with very robust, long-term efficacy, said Dr. Shadman, who noted that the toxicity profile is also well understood now (Burger et al., 2019; Table 2).

“Ibrutinib is also a very easy drug to start,” said Dr. Shadman. “You basically write the prescription and send the patient to the pharmacy to pick it up, assuming insurance is not an issue; it really is that easy.” (Since this presentation at JADPRO Live, acalabrutinib was approved, and Dr. Shadman adds that this applies to acalabrutinib as well.)

Although the combination of venetoclax and ibrutinib seems very attractive from the clinical standpoint and a number of studies investigate the regimen, in the first-line setting, this regimen is still experimental. Nevertheless, said Dr. Shadman, the data were impressive. Previously untreated high-risk, older patients administered 3 months of ibrutinib monotherapy followed by venetoclax combined therapy had a 1-year progression-free survival of 98% and an overall survival of 99% (Jain et al., 2019). In addition, 69% of patients had remission with undetectable MRD in bone marrow.

“The problem with this combination is that it leaves patients with limited options should pro-

Table 2. First Treatment Choice: Ibrutinib vs. Venetoclax Plus Obinutuzumab in the Front-Line Setting

Ibrutinib	Venetoclax plus obinutuzumab
Long-term efficacy data available	Time-limited treatment
Easier to start	Better tolerated and easier to continue
Preferred in patients who <ul style="list-style-type: none"> • Can't follow the ramp-up schedule for venetoclax • Have significant/unstable renal issues 	Preferred in patients who <ul style="list-style-type: none"> • Have cardiac issues (arrhythmia, hypertension) • Have bleeding issues
Studied against stronger regimens (FCR and BR)	Deep remissions (at minimal residual disease level), and would expect the same in younger patients
Venetoclax is effective at the time of ibrutinib progression	Less is known about effectiveness of ibrutinib after venetoclax progression

Note. FCR = fludarabine, cyclophosphamide, and rituximab; BR = bendamustine and rituximab.

gression occur,” Dr. Shadman observed. “While several studies have demonstrated that if ibrutinib stops working, then venetoclax is still a reliable back-up, there are not a lot of data at the time of this presentation about what happens if venetoclax stops working. These are all reasons to go with ibrutinib first.”

SIDE EFFECTS AND MANAGEMENT

As Ms. Goodrich reported, the risk of atrial fibrillation with ibrutinib is five times greater than that seen in the normal population. There is also a high rate of bleeding, although most of it is minor. Although hypertension is an initial problem, said Ms. Goodrich, the rate increases over time. There are also concerns about diarrhea, which can be a “life-altering side effect” for patients on ibrutinib.

“I tell patients to take ibrutinib at night, when their gut is shutting down, because they tend to have less nausea and diarrhea,” she explained. “Patients should be prepared for lymphocytosis, as well.”

Hyperglycemia is also something to keep in mind with patients who are on ibrutinib.

Approximately 50% of patients who discontinue ibrutinib do so because of toxicities, as opposed to approximately 21% of patients who discontinue due to progression (Mato et al., 2018). As Ms. Goodrich reported, next-generation BTK inhibitors like acalabrutinib carry a lower risk of bleeding, skin toxicity, pneumonitis, and a slightly lower risk of atrial fibrillation/atrial flutter. Hypertension is also less of an issue, said Ms. Goodrich, but the data still need to mature.

“Our first-generation drugs are always our breakthrough, but then our second-generation

drugs get smarter,” Ms. Goodrich explained. “Compared with ibrutinib, acalabrutinib has less off-target hits that cause platelet inhibition that leads to bleeding and atrial fibrillation. However, the risk of headaches is much higher on acalabrutinib than ibrutinib.”

Regarding venetoclax, Ms. Goodrich noted the risk of tumor lysis syndrome, which was fatal in early clinical trials. Venetoclax is now administered with a ramp-up aided by a “color-coded calendar” that makes it very easy for patients, said Ms. Goodrich. On the ramp-up schedule, the dose is gradually increased over 5 weeks to the full 400-mg dose.

“All dose escalations require some level of tumor lysis monitoring, and I think that was initially scary, but we are all using it because it is such an effective drug,” said Ms. Goodrich.

Dr. Shadman noted that the ramp-up protocol should absolutely be followed. The tumor lysis associated with venetoclax can happen very quickly in a high-risk patient, said Dr. Shadman. The right patients need to be selected, and patients need to be watched very closely for the first 4 to 8 weeks. After 2 months (including the 1 month debulking with an anti-CD20 antibody), however, the drug becomes easier to tolerate.

“Patients and providers must pay the price up-front with venetoclax, but they then enjoy a relatively easy drug after the initial storm,” Dr. Shadman observed. “However, in patients who logistically can't follow the ramp-up protocol or in patients who have significant or unstable kidney disease, ibrutinib/acalabrutinib would be a great choice.”

RELAPSED/REFRACTORY TREATMENT OF CLL

As Ms. Goodrich explained, because most patients do so well on BTK inhibitors or venetoclax, patients rarely have to go to the third line, but there are several novel agents available, including idelalisib, a PI3K inhibitor. Chimeric antigen receptor (CAR) T-cell therapy is not yet approved for CLL, Dr. Shadman added, but there are ongoing registration studies for CLL.

“For high-risk CLL patients, I would put CAR T-cell therapy in the same box as allogeneic stem cell transplant,” said Dr. Shadman. “If a patient gets to the point where I start considering stem cell transplant, then I will always use CAR T-cell therapy if I have access to it before doing a transplant” (Table 3). ●

Disclosure

Dr. Shadman has consulted and served on advisory boards for AbbVie, Genentech, AstraZeneca, Sound Biologics, Pharmacylics, Verastem, ADC Therapeutics, Collectar, Bristol-Myers Squibb, and Atara Biotherapeutics, and received research funding from Mustang Bio, Celgene, Bristol-Myers Squibb, Pharmacylics, Gilead, Genentech, AbbVie, TG Therapeutics, Beigene, AstraZeneca, Sunesis,

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Table 3. Novel Agents for Relapsed/Refractory Chronic Lymphocytic Leukemia

	Ibrutinib	Venetoclax	Idelalisib/Duvelisib
Target	BTK	BCL-2	PI3K $\delta/\delta + \gamma$
Dose	420 mg po daily	Ramp-up 400 mg po daily	150 mg po bid (idelalisib) 25 mg po bid (duvelisib)
Anti-CD20 antibody	No major benefit Faster “response”	Recommended R/R label	Yes for idelalisib
Major side effect (concern)	Bleeding (anticoagulation)	TLS (initially)	Colitis (diarrhea) Infections (FDA alert)
Other side effects	Body pain Fatigue Hypertension AFib	Neutropenia	Pneumonitis Transaminitis (idelalisib) PJP CMV
Duration	Indefinite	Fixed	Indefinite

Note. po = orally; bid = twice daily; Afib = atrial fibrillation; TLS = tumor lysis syndrome; PJP = *Pneumocystis jiroveci*; CMV = cytomegalovirus.