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Released: 10/28/2022
Valid until: 10/28/2023
Time needed to complete: 15 minutes

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Treatment of CLL/SLL with BTKis: Whole Patient Approaches

Announcer:
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Dr. Roeker:
Hello, I'm Dr. Lindsey Roeker from Memorial Sloan Kettering Cancer Center, and I'd like to welcome you to our Patient-Clinician Connection on BTK inhibitors in chronic lymphocytic leukemia, or CLL. Increased clarity on the pathogenesis of CLL and small lymphocytic lymphoma, or SLL, has led to the identification of active agents that target the B cell receptor signal. This means increased treatment options for patients. Novel agents that target B cell receptor signaling are improving progression-free and overall survival over chemoimmunotherapy. These include inhibitors of Bruton’s tyrosine kinase, or BTK, as well as BCL-2.

With the increased number of effective treatment options, therapy selection for patients has become increasingly personalized and dependent on patient preference as well as disease and therapy-related factors.

Today, I'll be illustrating my approach when discussing treatment options with a patient using 2 clinical vignettes. So let's get started.

Today, my patient Bill Johnson is in my office to discuss initial treatment options for his recently diagnosed CLL. Mr. Johnson is 68 years old and has a history of diabetes and well-controlled hypertension. On his physical exam, he has bulky bilateral axillary adenopathy, and his spleen extends 5 cm below his costal margin. His labs show that his white count is 82.4, his hemoglobin is 9.2, and his platelets are 87,000. He has unmutated IGHV and his FISH [fluorescence in situ hybridization] showed deletion of 17p. He does not have any other cytogenetic abnormalities.

Hi, Bill, it's really good to see you again. How have you been doing?

Bill:
Well, I'm really tired, especially at the end of the day.

Dr. Roeker:
Is it limiting you from doing things that you want to be doing?

Bill:
Well, yes, I really enjoy gardening, but I just don't have the energy to do that. And I don't feel like going out for a walk at night, or I don't really feel like doing anything.

Dr. Roeker:
Okay. So based on that fatigue, and then also some of the bloodwork results we have, I think it's time to start talking about treating your CLL. And as you might remember, we did some genetic testing during your last visit. One of those tests was called FISH. And it looks

for, basically, big missing pieces of your chromosomes. Your CLL cells have something called deletion of 17p, which tends to be associated with more aggressive disease.

Bill:
And when you say aggressive, that sounds really bad.

Dr. Roeker:
And I totally understand. When we only had chemoimmunotherapy, deletion of 17p was associated with disease that just really didn't respond very well or have very long-lasting remissions. But we now have drugs that work great regardless of kind of chromosomal abnormalities. So regardless of the genetic features, I want to reassure you that we have drugs that will work very well for treating the CLL.

Bill:
So how do we treat it?

Dr. Roeker:
There are 2 big options. The first is a pill-only approach that's a continuous treatment, meaning we use it for as long as it's working. The second is a combination of pill and IV treatments that we use for a year.

So when we think about that first option, there are 2 FDA-approved options called ibrutinib and acalabrutinib. And there's a third drug that's in the guidelines, but not yet FDA-approved. That's called zanubrutinib. And these are 3 medicines that are called BTK inhibitors. How they work is they basically cut off the signal in the cell that tells it to keep living and surviving and growing. So by cutting off that cell, it really prevents the cancer from growing. They're continuous medicines, which means you take them for as long as they're working.

The second option is a combination of a pill called venetoclax, and an IV called obinutuzumab. And those 2 medicines are used together for a combination of a year. After that year of therapy, you enter a period called treatment-free observation, which means the cancer is well controlled, and we don't need any therapy for some time afterward.

Bill:
So now does one work better than the other?

Dr. Roeker:
Great question. So the BTK inhibitors have longer-term data, longer follow-up to suggest that they work really well for patients with deletion of 17p. We know that for venetoclax and obinutuzumab, people who have this deletion of 17p tend to have their disease come back faster than those who don't have that genetic change after we stop treatment. But they've never been compared head-to-head. So we don't have data to say that one is definitively better than the other. Because of that, I really rely on you and the other medical problems you have and also your preferences to figure out which treatment option is really the best.

Patients with CLL who require treatment have several great treatment options. The preferred regimens that are listed in the NCCN guidelines include 3 BTK inhibitors. There's ibrutinib, acalabrutinib with or without obinutuzumab, and zanubrutinib, which isn't yet FDA-approved, but is listed in the guidelines and FDA-approved for other lymphomas. And then the BCL-2 inhibitor venetoclax in combination with obinutuzumab.

I want to walk you through some of the clinical trial results that inform how we treat CLL. The first agent that we'll talk about is ibrutinib. This is a first-generation BTK inhibitor and was compared to chlorambucil in the frontline setting in the study RESONATE-2 that we now have 7 years of long-term follow-up. This included patients who are over 65 with untreated CLL and no deletion of 17p. And this study demonstrated both a progression-free and overall survival benefit when compared to chlorambucil.

There then is a series of phase 3 studies that examine ibrutinib with or without a CD20 monoclonal antibody in combination with other chemoimmunotherapy regimens, and all demonstrate progression-free survival benefits. Some also demonstrate overall survival benefits.

So iLLUMINATE studied patients who are over 65 with untreated CLL or SLL, or patients who were under 65 with coexisting conditions. And in this study, ibrutinib with obinutuzumab was compared to chlorambucil with obinutuzumab, and demonstrated progression-free survival benefit.

ALLIANCE was a study in which ibrutinib was studied with or without rituximab and compared to bendamustine/rituximab in patients who were over 65 with untreated CLL. This demonstrated a progression-free survival benefit when compared to bendamustine and rituximab, though notably ibrutinib and ibrutinib/rituximab did not have any significant difference, demonstrating that rituximab is not

needed in addition to ibrutinib.

The FLAIR study looked at patients over 75 with untreated CLL and SLL and who did not have deletion of 17p. And in this study, ibrutinib with rituximab was compared to FCR and demonstrated a progression-free survival benefit. This was specifically limited to those who had unmutated IGHV.

Finally, the ECOG 1912 study examined patients who were younger, under 70, with untreated CLL and no deletion of 17p. In this study ibrutinib and rituximab was compared to FCR and demonstrated both progression-free and overall survival benefits in both mutated and unmutated IGHV.

Acalabrutinib is a second-generation BTK inhibitor that has been compared to chlorambucil and obinutuzumab in the ELEVATE-TN study. So in this study, there were patients who received acalabrutinib, acalabrutinib with obinutuzumab, and chlorambucil with obinutuzumab. These patients were all over 65 and had untreated CLL or SLL, or were younger and had coexisting conditions. This demonstrated a progression-free survival of the acalabrutinib arms compared to chlorambucil/obinutuzumab. Notably, the study was not powered to demonstrate a difference between acalabrutinib and acalabrutinib with obinutuzumab, but did demonstrate a progression-free survival difference between these 2 arms.

Zanubrutinib is another second-generation BTK inhibitor that was studied through SEQUOIA. This is a study where zanubrutinib was compared to bendamustine and rituximab in patients over 65 with untreated CLL, or patients who are under 65 and head coexisting conditions. And in this study, zanubrutinib was associated with a progression-free survival benefit.

Switching gears, venetoclax has been studied in combination with obinutuzumab through CLL-14. This is a 1-year fixed-duration study, and venetoclax with obinutuzumab was compared to obinutuzumab with chlorambucil in patients with untreated CLL and a CIRS score greater than 6. Here we see a progression-free survival benefit with the combination of venetoclax and obinutuzumab.

Notably, venetoclax-containing regimens have not been compared directly to BTK inhibitors in any prospective studies.

While the BTK inhibitors have not been compared directly in the frontline setting, they have been compared in the relapse setting. The first study I'll highlight is ELEVATE-RR, in which acalabrutinib was compared to ibrutinib. This was a phase 3 noninferiority study in patients with previously treated CLL. With immediate follow-up of 40.9 months, we see that median progression-free survival in both arms is 38.4 months. So the noninferiority endpoint was met. Atrial fibrillation rates were compared for those treated with acala in which the rate was 9.4%, versus ibrutinib, where the rate was 16%. This was a significant difference. The treatment discontinuation rates due to adverse events was also different between the arms. So 14.7% of acalabrutinib-treated patients, versus 21.3% of ibrutinib-treated patients discontinued due to toxicity. The rates of grade 3 infections and Richter's transformation were similar between the arms, and median overall survival was not reached in either arm.

ALPINE is the second study comparing BTK inhibitors that I'd like to highlight. In this study, zanubrutinib was compared to ibrutinib in a phase 3 study of previously treated CLL patients. With a median follow-up of 24 months, the 12-month landmark event-free rate was 94.9% in zanubrutinib-treated patients, versus 84% in ibrutinib-treated patients. The atrial fibrillation rate was different between the arms, so it was 2.5% in those treated with zanubrutinib versus 10.1 for those treated with ibrutinib. The overall response rate in patients with deletion of 17p was 83.3% for those treated with zanubrutinib versus 53.8% for those treated with ibrutinib.

With a number of effective therapies, selection of therapy is really driven by patient disease characteristics, as well as the treatment characteristics. So that includes the administration, the duration of treatment, and the toxicity profiles, as well as patient comorbidities and their preferences.

The patient that we'll be seeing today has the deletion of chromosome 17p, which continues to be a challenge in CLL.

We know that there are inferior results for those who have deletion of 17p or TP53 mutations. Ibrutinib has been studied in a number of different ways. We have a phase 2 pooled analysis that included 89 patients across 4 studies and showed that the 4-year overall survival rate is 88%. So there are long-term data demonstrating effect. We've also had real-world evidence, including a study of 110 patients with TP53 aberrations that demonstrated lower overall survival and progression-free survival benefit versus those who do not have a deletion of 17p.

For acalabrutinib, ELEVATE-TN included patients who had deletion of 17p, and this was 14% of the population. In this patient population, the 48-month progression-free survival was 75% with those treated with acalabrutinib and obinutuzumab, versus 76% for those who received acalabrutinib monotherapy.

Zanubrutinib has also been studied in non-randomized cohorts of patients who have deletion of 17p. So there's a non-randomized cohort of patients who receive zanubrutinib monotherapy. And those patients have an overall response rate of 95% and an 18-month

progression-free survival of 89%. The 18-month overall survival rate is 95%.

Finally, venetoclax was studied in CLL14 and included patients with TP53 aberrations. We see that the progression-free survival is less durable in
patients who have TP53 aberrations versus those without.

So when thinking about selecting treatment, it's important to discuss potential toxicities as these are often deciding factors based on patient preference. So let's watch as I discuss these with Bill.

So each of these treatment options have different side effects, and which one we pick really depends on your lifestyle and your other medical problems. So to help me understand what would be a better fit, can you tell me about what you like to do and what your priorities are?

Bill:
Well as you know, I still work driving a bus. And until recently, I've been doing that around 4 days a week, 8 hours a day. And on the weekends, I enjoy gardening and hiking, but I really don't have the energy to do any of that anymore. And I really would like to just get back to doing those things. You know, with the kids grown and, you know, out of the house, my wife and I, we like to travel. And, you know, I have my daughter and my only granddaughter who both live out of state, and it would be nice just to go see them again.

Dr. Roeker:
Yeah, of course. So when I think about each of these medicines, they have just different side effects. So the BTK inhibitors are, like I said, pills that you're taking once or twice a day. They have some side effects that they all share in common. And then each of the drugs have some more specific side effects.

So as a class, the major things I think about are atrial fibrillation, which is an abnormal heart rhythm. So if you were to feel palpitations, chest pressure, shortness of breath, anything like that, I'd want to know about it, because atrial fibrillation is associated with a risk for stroke. So if you're having atrial fibrillation, I want to make sure that we're managing it appropriately.

The second piece is hypertension or high blood pressure. So we'll watch your blood pressure carefully while you're on these medicines. Some people require either addition of a new blood pressure medication or increasing the dose of the existing blood pressure medications.

The third thing I think about is bleeding. If you are noticing blood anywhere, blood in your urine, blood in your stool, coughing up blood, throwing up blood, I definitely want to hear about it right away. We also ask that you let us know anytime you're going to have a procedure or surgery because we need to hold the medications before and after to make sure that those are safely done.

With venetoclax and obinutuzumab, the venetoclax major side effect that we think about is something called tumor lysis syndrome. And that's basically where the cells pop open as they're dying, and they release all of the salt into your bloodstream. That can be really hard on your kidneys. So to minimize that risk, we start at a low dose and we build up the dose over a 5-week period. With each of those dose escalations, we check your labs before your dose, after your dose, and the following day to make sure that it's done safely. We also make sure that you're staying really well hydrated, sometimes with IV fluids, to really help that process

With obinutuzumab, the major side effect is infusion-related reactions. And that happens while you're receiving the infusion in our infusion suite. So that can feel all sorts of different ways, but if you're having any feeling that something isn't right at all, you let our nurses know, we stop the infusion, give you medicines to calm down your immune system, and then restart at a slower rate.

And the combination of venetoclax and obinutuzumab also can cause the blood counts to go down. So we watch the counts carefully and make sure that we're doing everything we need to to support you through this time to make sure that it's done safely.

Bill:
So each comes with some good and some bad.

Dr. Roeker:
Yes, absolutely. And it's really deciding which of these approaches better fits in your lifestyle.

For the BTK inhibitors, I think about class effects, and then I think about the specific toxicity profile of each agent. So the class effects are atrial fibrillation, hypertension, and bleeding risk, as well as the risk of infections. Ibrutinib tends to have more off-target effects with addition of myalgias and arthralgias, as well as rash. Acalabrutinib has an associated headache, which tends to occur at the beginning of therapy and wanes over time. And then zanubrutinib is associated with a bit more GI toxicity, as well as cytopenias.

Venetoclax and obinutuzumab have an entirely different profile. And in order to administer this therapy safely, it's really 9 weeks in a row

at the beginning of treatment where patients require 1 to 2 days of visits a week. So venetoclax, the major side effect is tumor lysis syndrome. And to mitigate the risk of tumor lysis syndrome, we start at a 20-mg dose level, and we ramp up over 5 weeks to the final dose of 400 mg. With each of these dose escalations, there's a requirement for pre-dose labs as well as post-dose monitoring and appropriate hydration based on a patient's tumor lysis risk.

With obinutuzumab, the major side effects are infusion-related reactions, which tend to be fairly common, as well as cytopenias. Because of the combination of IV therapy and then the 5-week dose escalation, it's a 9-week period where patients do require that intensive monitoring or in-office care.

We also think about the time-limited versus continuous approaches, and those really do affect patients' decisions. So BTK inhibitors are continuous, whereas venetoclax and obinutuzumab has been studied as a one-year fixed duration.

So in general, when I'm thinking about selecting initial therapy, I think about a patient's comorbidities. I think about whether they have preexisting atrial fibrillation or uncontrolled hypertension, and I think about other blood thinners or requirements for antiplatelet agents. I also think about patients who have renal impairment and the effect that that might have on a venetoclax dose escalation.

Beyond the specific side effect profiles, I also think about the differences between time-limited therapy with venetoclax and obinutuzumab, versus continuous therapy with the BTK inhibitors, as these often influence patient decision-making as well.

I think about their disease characteristics, including whether they have a TP53 aberration. I think about their comorbidities. So does the patient have uncontrolled atrial fibrillation, uncontrolled hypertension, a high risk of bleeding with maybe concurrent anticoagulation or antiplatelet drugs, or does the patient have renal dysfunction, which may make a venetoclax dose escalation more complicated?

The final piece that we think about is how to sequence therapies effectively, and really a lot of the sequencing decision-making has to do with what a patient received in the frontline setting. So if patients received a BTK inhibitor in the frontline setting, the next line of therapy really depends on why they discontinued the therapy. Is it a patient who discontinued for toxicity, in which case trying a different BTK inhibitor is an option? Or is it a patient who progressed on a BTK inhibitor in which case changing to a venetoclax-based regimen is the most appropriate decision-making?

If a patient received frontline venetoclax and obinutuzumab, the options either include a BTK inhibitor so you can switch classes, or if a patient completed their frontline fixed-duration therapy and had a period of benefit afterward, there's also consideration for venetoclax re-treatment, which has been studied in real-world series and shown to be an effective strategy. PI3K inhibitors are also FDA-approved for the treatment of CLL and can be used in the third-line setting or beyond.

So the key takeaways are that BTK inhibitors and venetoclax and obinutuzumab have not been studied head-to-head but are 2 effective options for the treatment of CLL in the frontline setting. And decision-making about which therapy is best is really dependent on patient preference, comorbidities, and genetic features of their disease. The adverse event profiles for these 2 approaches are very different and should be discussed with patients to determine which one is the best fit.

Thank you so much for your time and attention, and I hope this is a helpful tool in your clinical practice.

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