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Navigating Treatment Sequencing After Frontline Treatment Failure in CLL

Announcer:
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Dr. Mencia:
Hello and welcome. Today we will be discussing treatment sequencing after frontline treatment failure in chronic lymphocytic leukemia. I'm Dr. William Mencia, and here with me today is Dr. Jennifer Brown.

Dr. Brown, let's get started. How do we distinguish between resistance and intolerance to treatment in patients with CLL?

Dr. Brown:
This is a very important question, which has really arisen as we developed BTK inhibitors as continuous therapies. When you're asking patients to stay on therapy for years at a time, naturally, some side effects might emerge that will cause them to need to come off therapy, and so this is where it became really essential to distinguish patients who discontinue a continuous BTK inhibitor for an intolerance event, like an adverse event, when their disease is probably still sensitive to that drug versus those who have disease progression during therapy with the drug, who we would say are resistant to the drug. And as we now know, many of those who develop resistance while taking a BTK inhibitor have a BTK resistance mutation. Whereas most who stop for intolerance do not have a resistance mutation and, in fact, can later be retreated with the same class of drug. Whereas patients who have true resistance—whether or not they have a mutation, but if they have a mutation, that strengthens the case that they have true resistance—should not be retreated with the same class.

Now for venetoclax, our one BCL2 inhibitor therapy that we have right now, it's a little bit different because we're mostly using that as a time-limited therapy, so most patients are able to finish therapy and stop, and then if they relapse some length of time later, we assume that they're probably still sensitive to the drug.

And so patients are not usually stopping a 1-year venetoclax regimen for intolerance. It can happen though, and if they do, then that's something that could potentially allow re-treatment. Progression during the 1-year regimen is very unlikely too. So we tend to look more at the timing of progression after stopping those regimens. If it's only been a few months or 6 months, we'll generally view the patient as having resistant disease, but the longer, the more years, the better in terms of retaining sensitivity.

Dr. Mencia:
Thank you, Dr. Brown. Let's talk now about measurable residual disease, or MRD. It seems that MRD is becoming increasingly central

in how we think about CLL care. After frontline treatment, how does MRD help clinicians decide what to do next, and how are trials like FLAIR and SEQUOIA shaping that thinking?

Dr. Brown:
So MRD or measurable residual disease is a way that we check to see if there are any detectable CLL cells remaining, classically at a level of one in 10,000 cells. But now we also have next-generation sequencing assays that can detect down to 1 in a million cells. And these have been developed mostly because we have increasing interest in time-limited regimens, because most patients prefer that. And we know that with time-limited regimens, if you can get to undetectable MRD by whichever assay is being used, you'll have a longer progression-free survival, and in some studies, a longer overall survival than if there's still detectable disease.

Right now we've been mostly using it to assess prognosis in that way, but there is increasing interest and desire to use it to guide duration of therapy. And in particular, the FLAIR trial, which was published last year, used an MRD-guided approach where they determined how long it took patients to get to undetectable MRD the first time, and then they treated them for that same duration of time again. So if it took 1 year to get to undetectable MRD, they gave them another 1 year of therapy for a total of 2 years. So the therapy duration was a little bit longer. It was about 27 months on average.

But what was really striking in this study is that patients who received this MRD-guided ibrutinib-venetoclax regimen, had a longer overall survival than those who had continuous single-agent ibrutinib. Not just progression-free survival, but overall survival. And that, as we know, was not seen when the standard 15-month regimen of ibrutinib-venetoclax was compared to ibrutinib in CLL17, as we just heard reported at ASH and has also been published in *The New England Journal of Medicine*.

One of the complexities around incorporating this MRD guidance into our trials is that many studies have used different approaches. And so SEQUOIA, for example, used zanubrutinib-venetoclax, but they had very, very stringent criteria for the MRD guidance, so most of the patients stayed on treatment. Only 11% of them so far have stopped the zanubrutinib. And so now in the NCCN Guidelines, for example, we have several specific MRD-guided regimens based on results that have been published. But there's a lot of ongoing research and interest in figuring out what the best way to do this is that's also reasonably simple and manageable in a community setting.

Dr. Mencia:
That's really helpful, Dr. Brown. So when a patient with CLL progresses after frontline therapy. Choosing the next treatment can get complex.

So how does a patient's prior therapy, be that with a BTK inhibitor, a BCL2 inhibitor, or chemoimmunotherapy, how does that shape your approach to second-line treatment? And what guidance would you offer to community clinicians who are trying to navigate sequencing in real-world practice

Dr. Brown:
So the simplest way of viewing this is that if patients had a BTK inhibitor frontline, they can potentially switch to a BCL2 inhibitor-based regimen second line. Or if they had a BCL2 inhibitor regimen frontline, they can switch to a BTK inhibitor second line. That's not wrong, but there's a lot more nuance associated with it potentially.

And so, for example, if patients had a BTK inhibitor frontline and stopped for intolerance, as we were discussing before, they could still do another BTK inhibitor later. They could do one that's better tolerated like a second generation, for example. If they stopped for progression, though, active progression on the BTK inhibitor, then it's really necessary that they switch to a venetoclax-based regimen because there's a good chance they have a mutation that may make them resistant to most of the other covalent BTK inhibitors.

We do now have pirtobrutinib, which just had an expansion of its approval to include anyone with prior covalent BTK inhibitor exposure. And so that's also an option in a person who's progressed on a covalent BTK inhibitor. But for now, I think we're mostly using venetoclax in that setting.

And then similarly, if patients had a time-limited venetoclax regimen and they've been off treatment for a long time, you know, if they've been off 5, 7 years, had a very long duration of remission, just repeating the same regimen has a lot of appeal for those patients because they're likely to still be sensitive to it, and then you still save BTK inhibitors for later.

With respect to prior chemoimmunotherapy, which we're having fewer and fewer patients who had prior chemoimmunotherapy, although there's still some, they can do anything. We have actually our largest body of data on the efficacy of BTK inhibitors and time-limited venetoclax-based therapy in that setting, patients who'd had 1 prior chemoimmunotherapy regimen.

So it's a good opportunity to talk to the patient about what they're interested in and their values about treatment.

Dr. Mencia:
Well, that's really practical advice. Thank you, Dr. Brown. Another consideration is reassessment of biomarkers. So when and how do you retest, and how do those results guide subsequent treatment decisions?

Dr. Brown:
Right, so our most important biomarkers are IGHV, P53, and we're increasingly interested in complex karyotype, as well. So IGHV, the good thing about that is you can check that once at diagnosis or prior to first-line therapy, and that's stable, so we don't have to check that again over the course of the illness.

But the mutation panel for P53 and the FISH panel, those can evolve over time. And so we all recommend checking those before every next line of therapy to see if they've been acquired. And remember, FISH and mutation panel are both required to assess P53 status because there can be deletion of the short arm of 17P, which is detected by FISH, or there can be a mutation of P53, which is detected by a sequencing panel.

So both of those are required and prior to any next line of therapy. And then in terms of the karyotype complexity, that's also something that can change and evolve and worsen over time. And so we do recommend that also prior to each line of therapy.

Dr. Mencia:
That's fantastic. Thank you.

Let's close this session with a discussion about shared decision-making. How do we balance our guideline-driven treatment recommendations with real-world patient factors such as quality of life, goals, and logistical considerations? How do you have these discussions with your patients, and what insights can you provide our learners on finding that balance when making second-line treatment decisions?

Dr. Brown:
And so I always have a discussion with the patient about what their various options are because there are usually many. There may be a BTK-based option; there may be a venetoclax-based option. We always have clinical trials. And so when you start talking to patients about this, you can discern how they feel about things, like some patients don't really mind if they're on a pill indefinitely if it means they don't have to come in to the doctor very much, and then they can travel and go wherever. Others would really prefer to just get something done and then be off treatment, hopefully for many years, and they don't mind that they have to come in 8 straight weeks to the clinic. So that's sort of the most stark consideration.

And some patients have actually strong opinions about the different side effect patterns, that they're particularly worried about atrial fibrillation, for example. And so we prefer not to do a BTK inhibitor. But maybe you think a BTK inhibitor is the best treatment option because they have higher-risk disease with P53 aberrations. So then you have to sort of balance that.

For the vast majority of patients, though, in second line, if they've had a good remission to first line, they still have a good number of options. So it's quite reasonable to take into account how they're feeling about things and whether they are traveling for the winter or going on a trip in a few weeks. The younger ones tend to prefer doing the time-limited therapy, even though it's a little more intense up front in my experience.

Dr. Mencia:
Well, we're just about done here, but before we wrap up, Dr. Brown, if you could leave the audience with just one take-home message from today's discussion, what would that be?

Dr. Brown:
Well, we have so many options for our CLL patients now and they're constantly expanding. And one shorthand way of thinking about it is whatever they had first line switch to the other second line.

Dr. Mencia:
All right, well that's all of the time we have, so I want to thank our audience for participating and a big thank you to you, Dr. Jennifer Brown, for joining me here and for sharing all of your valuable insights with our audience. It was great speaking with you today.

Dr. Brown:
My pleasure.

Announcer:
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