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Sequencing CLL Therapies: A Guide to First-Line, Second-Line, and Beyond

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Lilly. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss how we sequence therapies for patients with chronic lymphocytic leukemia, or CLL for short, are Drs. Seema Bhat and Joanna Rhodes. Not only is Dr. Bhat an Associate Professor in the Department of Internal Medicine in the Division of Hematology at Ohio State University, but she also specializes in treating patients with CLL at the Ohio State University Comprehensive Cancer Center – James. Dr. Bhat, thanks for being here tod

Dr. Bhat:
Thank you for having me today.

Dr. Turck:
And Dr. Rhodes is the Director of Lymphoma at Rutgers Cancer Institute of New Jersey and New Brunswick. Dr. Rhodes, it's great to have you here with this as well.

Dr. Rhodes:
Thanks for having me.

Dr. Turck:
So if we start with you, Dr. Bhat, would you break down for us the therapies that are currently available for patients with CLL?

Dr. Bhat:
Yes, of course. We are in very exciting times as far as CLL therapies are concerned. Lots has changed in the last decades. We have moved completely away from chemoimmunotherapy, which used to be the standard of care in the past. Treatment has moved to what we call targeted agents. And of these, we have two different classes of targeted agents. The first one is BTK inhibitors, or Bruton's tyrosine kinase inhibitors. And we have them further divided into covalent and non-covalent. In the covalent group, we have ibrutinib, acalabrutinib, and zanubrutinib. And in the non-covalent, we recently had the first one approved, and that's pirtobrutinib, which can be used in the relapsed/refractory setting. Within the BCL-2 inhibitor class, we have venetoclax. And this is usually given in combination with an anti-CD20 monoclonal antibody in the frontline setting with obinutuzumab.

Dr. Turck:
Now if we turn to you, Dr. Rhodes, and zero in on the optimal sequencing of those therapies, what's the typical approach and treatment goal in the first-line setting?

Dr. Rhodes:
So when I think about my goals for patients with CLL, we know that it's not a disease that we can cure with our current treatment strategies, but it is a very treatable disease. So the first step is really making sure that we've controlled the symptoms that patients are having related to their CLL treatment. In the frontline setting, we have a lot of different grade options. And so this really is a long conversation, taking into account what patients would like to do, what their genomics and their genetics and their prognostic markers are, taking into account their comorbid medical conditions, and any other medications that they may have that could potentially interact or be challenging to give some of our new CLL targeted agents.

In the frontline setting, we really have two major groups of medications. As Dr. Bhat has mentioned, we have fixed duration of venetoclax and obinutuzumab, which is given for one year of therapy. And then we also have our covalent BTK inhibitors, which are given continuously for continuous disease control. Those medications can be given until the CLL progresses on treatment or if patients have a side effect or are so-called intolerant to the medications; we can stop the medications at that point and potentially monitor them off of treatment.

Dr. Turck:
And what are some considerations we should keep in mind in the second-line setting, Dr. Rhodes?

Dr. Rhodes:
Absolutely. So I think really it has to do with what our patients receive in the frontline setting and how well they respond. For patients, for example, that receive a fixed duration of venetoclax and obinutuzumab, I take into account how long it takes for their disease to come back when trying to decide whether or not I should be doing re-treatment with venetoclax versus switching classes and going to a covalent BTK inhibitor, such as acalabrutinib or zanubrutinib.

For patients that were treated with chemoimmunotherapy, venetoclax or covalent BTK inhibitors are both great choices, and really then we're starting to think about what works for patients, whether or not they want continuous therapy or fixed duration. What are their other medications? What other medical conditions do they have that we need to be mindful of when we're titrating these medications and putting them on board? And I think a lot about patient lifestyle, and I think patients really have a lot of say in what we're doing these days for their treatment because there are just so many great options.

And then for patients that receive continuous BTK inhibitor therapy in their frontline setting, the first question I'm asking is, why did they stop? Did their disease progress through it, or are they intolerant to therapy? For patients that progress through a covalent BTK inhibitor, I'm reaching for a venetoclax-based regimen in the second-line setting. And that's because we know that patients who progress on a covalent BTK inhibitor are unlikely to respond to another covalent BTK inhibitor. For patients that stop covalent BTK inhibitors for adverse effects or side effects or due to intolerance, as you'll see us say a lot in the literature, those are patients that I might try an alternative BTK inhibitor. So for example, if somebody was on ibrutinib and has a side effect that they can't tolerate, I may try acalabrutinib or zanubrutinib to see if that will work for them.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Drs. Seema Bhat and Joanna Rhodes about treatment sequencing in chronic lymphocytic leukemia care.

Now, Dr. Bhat, if the first- and second-line therapies end up being ineffective or tolerability is an issue for the patient, what would salvage treatment for patients with CLL look like?

Dr. Bhat:
This is a growing concern in our clinics. And there's a growing population of patients who have used both BTK inhibitors and the BCL-2 inhibitor venetoclax. We call them dual-refractory or dual-exposed patients. And we have very limited choices at this time for them. However, I'm very happy to say that recently, in December of 2023, we had the first non-covalent BTK inhibitor, pirtobrutinib, approved, which is approved for this population of dual-refractory CLL patients. And it has really good responses, and it's very well-tolerated.

The other agents are still in clinical development, and I'm excited about two types of treatment. The first one is epcoritamab, which is a bispecific monoclonal antibody, which is targeted against two different antigens: CD30 and CD20. And some of the first data in CLL were presented at one of the major conferences in 2023, where it was shown that the results were great in patients with dual-refractory CLL, and some of them, one-third of those patients, had complete responses. So we are very excited about that agent. And clinical trials with this agent are moving along both as single-agent and in combination with some of these other targeted agents.

The other type of therapy that I'm excited about and is moving along in clinical trials is CAR-T therapy for relapsed/refractory CLL patients, especially for these dual-refractory, highly pretreated patients.

Dr. Turck:
Well, we've covered a lot today, so before we close, I want to hear some key takeaways from each of you. Starting with you, Dr. Bhat, what would you like our audience to remember about the strategy behind the sequencing of CLL therapies?

Dr. Bhat:
I do want my patients to know that they have a lot of choices and lots of agents available if and when they need treatment. And most of the patients when they start treatment, whether they start treatment with a BTK inhibitor or a BCL-2 inhibitor, they will be very well-tolerated and they will live a near-normal life without any major side effects with these agents. And if the disease progresses on one

agent, typically each of these agents gives a long time before the disease needs another form of treatment.

And if and when that happens, they can go onto another line of treatment, and with this kind of sequencing, the overall lifespan of our patients is extended. And not just the lifespan, the quality of life of the patients is also improved because these agents are very well tolerated and patients can be near functional, living their normal lives with their family.

Dr. Turck:
And Dr. Rhodes, I'll give you the final word.

Dr. Rhodes:
So when I think about sequencing, I think about what we've chosen in a long discussion with our patient about what's best for them in frontline therapy and then really tailoring second- and third-line and beyond to that particular patient based off of their genetics, other medications, comorbid medical conditions as well as their lifestyle. Again, we're thinking really about how we utilize all of the different medications that we have out in our armamentarium for patients with CLL and how we do that over time.

Dr. Turck:
Thank you both. Those are some great comments for us to think on as we come to the end of today's program. And I want to thank my guests, Drs. Seema Bhat and Joanna Rhodes, for joining me to discuss treatment sequencing for patients with chronic lymphocytic leukemia. Dr. Bhat, Dr. Rhodes, it was great having you both on the program.

Dr. Rhodes:
Thank you so much for having us.

Dr. Bhat:
Thank you so much for having me.

Announcer:
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