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Diving Into Fixed Duration Therapy in CLL: Opportunities & Challenges

Announcer:
Welcome to *Project Oncology* on ReachMD. This episode is sponsored by Abbvie and Genentech. Here's your host, Dr. Jacob Sands.

Dr. Sands:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and joining me to explore opportunities and challenges with fixed duration therapy for patients with chronic lymphocytic leukemia, or CLL for short, is Dr. Elizabeth Brém. Dr. Brém is an Assistant Professor in the Division of Hematology/Oncology in the Department of Medicine at University of California Irvine School of Medicine. Dr. Brém, welcome to the program.

Dr. Brém:
Happy to be here. Thanks for having me.

Dr. Sands:
So let's begin by looking at how we treat CLL with fixed duration regimens in the frontline setting. Dr. Brém, how has this approach impacted the CLL treatment landscape?

Dr. Brém:
So it's kind of interesting. I feel like we went from fixed duration therapies to indefinite, and we've kind of swung back towards fixed duration therapies. Because if you go back five, six years ago, there was still a lot of use of chemoimmunotherapy in the frontline setting. Regimens like BR or FCR. And then subsequently, we've had studies, one from the Alliance group, one from the ECOG group looking at ibrutinib BTK inhibitor versus combination chemoimmunotherapy. And then one of those studies was done in younger populations with FCR as the control and another one was done in older populations using BR is the control. And in both of those studies, that progression-free survival, which was the primary endpoint, was improved with the use of BTK inhibitor over chemoimmunotherapy. So there kind of has been the swing from kind of fixed duration chemoimmunotherapy towards indefinite BTK inhibitor.

Then we got data from CLL-14, looking at obinutuzumab with venetoclax, and that kind of fixed duration two-year therapy. Now we don't have data looking at that combination of venetoclax/obinutuzumab versus chemoimmunotherapy nor do we, well, chemoimmunotherapy that many people would use routinely in clinical practice, it was compared to chlorambucil obinutuzumab, which most people wouldn't choose to use in their routine clinical practice.

And we don't have status studies to date looking at venetoclax versus BTK inhibitors. But certainly the response rates when you look at the venetoclax/obinutuzumab with all of the caveats of cross trial comparisons, looks at things like the overall response rate, progression-free survival is fairly similar. You can boil it down and look at some smaller subgroups if you like, but obviously those were all not pre-specified. In the convenience of that kind of two-year fixed duration therapy using a novel agent with a venetoclax, we're now seeing a little bit of a swing back towards fixed duration therapies.

And I think now the big debate is, are you going to use venetoclax/obinutuzumab, or are you going to use a BTK inhibitor? And what are the pros and cons of those two different approaches?

Dr. Sands:
So with that as a backdrop, can you outline some of the challenges you've encountered with fixed duration therapy?

Dr. Brém:
So if there's a downside to the fixed duration therapy, one of that is the obinutuzumab is an I.V. It's an infusion, patients have to come in

and get an infusion. And for a long time, I would have told you I don't think that's a huge barrier, particularly given that eventually it's a once-a-month infusion. But COVID I think has made things a lot more complicated. Obviously, there's some patients have been hesitant to come into the medical center at all. I have plenty of patients who would love to just see me over video visits and do oral therapies. So you have now the complication of some patients just not feeling comfortable coming in for an infusion.

So, pre-COVID, I would have told you again that I don't think the infusion is a huge barrier. I think it's become more of a barrier during the pandemic. So if there's a huge barrier to using this kind of fixed duration therapy, it's that one drug is I.V. and involves the infusion center.

I think the other, I'll say barrier, although it's more of a knowledge gap than a barrier, is patients with unmutated IGVH maybe didn't do quite as well as their mutated counterparts in the CLL-14 study. There were very few patients with for example, 17p deletions or TP-53 mutations in CLL14, which I think limits the ability at which we can extrapolate the outcomes to those particular populations.

Dr. Sands:
Now, with that being said, how does fixed duration therapy differ from standard of treatment approaches, like the treat-to-progression therapies, for example? Do the opportunities outweigh the challenges you just discussed?

Dr. Brém:
I think it depends a lot on the patient in front of you. But certainly, for some patients, the idea of an indefinite therapy is really stressful to them, it makes them concerned they're going to get more treatment than they need, worries about long-term toxicities. And so in that case, it's absolutely an opportunity in that it makes the idea of treatment much more acceptable or seeming reasonable to some patients.

I think this is an evolving field, that, you know, with the kind of treat-to-progression, it's truly that. It's treat until clinical progression, whether that be the patient starts to have symptoms, the white count goes up, their anemia gets worse, what have you. And in the fixed duration, it's also essentially that. The patients were studied for two years, and that was the end of therapy.

Now, we do have some data on minimal residual disease negativity rates in the fixed duration therapy patients and the CLL-14 study. But that wasn't used to guide therapy. And studies that are ongoing now looking at fixed duration therapies, or there's really some interesting study designs where one cohort gets a fixed duration end of statement, and one cohort is MRD-guided that I think all of this has potential to become potentially MRD-directed therapy based on how some of these studies shake out.

And this is actually one of the things I talk to my patients about before we start particularly indefinite therapy is that, yes, today, the plan would be to treat you until intolerance or clinical progression. But that data may evolve from some of these studies, where we'll learn that a population of patients who, for example, are MRD negative in their bone marrow may be able to stop therapy at some point.

So I think this is a very fluid conversation that I think has the ability to change quite a bit over the next year or two based on some available data.

Dr. Sands:
For those just tuning in, you're listening to Project Oncology on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Elizabeth Brém about fixed duration therapy in CLL. So, Dr. Brém, let's consider the patient's role in all of this. Starting with the patient profiles, how do they help us determine whether fixed duration therapy is right for our patients?

Dr. Brém:
So I think there's two things you have to think about in terms of the patient profile when you're kind of answering this question. So one thing is about the characteristics of the disease itself. So the two things that kind of stick out in my mind are IGVH status. And there's some concern that when you look at the CLL-14 data, looking at the combination of obinutuzumab with a venetoclax, that maybe the patients who had unmutated IGVH didn't do quite as well as the mutated counterparts. Now, that wasn't a pre-specified endpoint, things weren't stratified based on this, so maybe these aren't conclusions that we should be making based on that data. And I do think that for a patient in that situation, it's kind of a conversation about the pros and cons of one approach versus the other.

The disease population, which I do have a personal bias, is those with a TP-53 mutation or 17p deletion. There weren't many of these in the CLL-14 study. I think if you look, it's about 10 percent of patients had some sort of mutation TP-53. And those patients don't seem like they did quite as well with the venetoclax/obinutuzumab combination. Now again, the comparator arm was obinutuzumab/chlorambucil. But we do have years of long-term data now with this subgroup with BTK inhibitors and many of them can do very well for a long time. And this is a population that did historically very poorly with combination chemoimmunotherapy. So if the patient did have a 17p deletion or a TP-53 mutation in their disease, in that situation, I actually really would be biased towards a BTK inhibitor.

In the absence of that, I think it's a real conversation. I found that in many cases, myself, and really the patients too, may bias towards a fixed duration approach for our younger patients. When you're talking about indefinite therapy for someone in their 50s, or 60s, without really many other comorbidities, you could be talking about a fairly long time. And not to say that that's not a good thing, because it implies a long duration of disease control. But we do know that with BTK inhibitors, there are certain toxicities that seem to come up over time. So you may wish to avoid those with our patients who are younger, with comorbidities.

I find that for the older patients, many of them, it's not to say that the fixed duration is not desirable, but the whole idea of coming in for an infusion and the busyness of coming back and forth. And also maybe potentially dealing with either a hospitalization or very close monitoring upfront for the risk of TLS with a venetoclax, that becomes undesirable. And those patients we may bias towards a

BTK inhibitor. But I'd say in general, for most patients, it really is a conversation. And it's going through the pros and cons of both approaches.

Dr. Sands:
So an important part of the art of medicine is to take all of this science and data and distill it down for the individual in front of us. So how can we integrate our patient's individual goals into the decision-making around fixed duration therapy?

Dr. Brém:
So I think that for some patients, the goal is to interface with the medical establishment as little as possible. Some patients just love the idea of taking a pill and checking in periodically and that it makes them feel like they're not sick. And so I do think that those are patients where you can say, 'Look, we have years of evidence with BTK inhibitors, they're very effective, they have a good duration of therapy, and you know, for you, a BTK inhibitor that you can just sort of take it home, not have to worry about infusions, not have to worry about TLS risk,' that fits that patient's goals.

And then you have other patients who they really love the idea of not having to deal with this for a protracted period of time, that they could do therapy for some amount of time and just be done with it, and then move on with their life knowing that, you know, as we always counsel patients, CLL does unfortunately have a pesky way of showing up again, but who the heck knows what we'll be doing for this disease seven, eight, nine, ten years down the line. So for some patients, just dealing with it for a confined amount of time, knowing that there's an endpoint, knowing it's going to be over is really, really appealing. And for those patients, I mean, CLL-14 really did show an excellent PFS benefit in the venetoclax/obinutuzumab arm. I mean, in general, again, with all of the caveats of cross trial comparisons, when you look at basically all of the well accepted, upfront approaches for CLL, whether it's venetoclax/obinutuzumab, whether it's BTK inhibitors, they all really have very similar progression-free survival, the two years they all have very similar overall response rates. And so there probably isn't a wrong choice in the bunch. It really is, as you say, kind of thinking about the patient in front of you and what that patient's particular goals are.

Dr. Sands:
Now we're almost out of time. But before we wrap, Dr. Brém, can you tell us how we can better facilitate decision-making conversations with our patients?

Dr. Brém:
The million-dollar question. I think it's really about, you know, as we're sort of pointing out is that different patients have different goals and different values and different priorities. And I think that any opportunity you have to kind of suss some of those things out before you have the conversation about treatment really can be beneficial. I find in general that if I've at least had one other visit with a patient before we're kind of having this conversation, I kind of have a thought about which way this patient is probably going to feel more comfortable or want to go based on kind of the interaction that I've had to date. And then you can kind of really, I think, it facilitates or makes your shared decision-making a lot easier.

I guess my two thoughts would be spend some time or do the best you can to kind of understand the values of the patient going into the conversation. And then the other piece would be, do your best to kind of put yourself in their shoes and kind of think about what the day to day or what those several weeks, particularly the beginning therapy is going to look like and how someone might want to incorporate that into their life.

Dr. Sands:
Well, with those pieces of advice in mind, I want to thank my guest, Dr. Elizabeth Brém, for joining me to discuss fixed duration therapy for patients with chronic lymphocytic leukemia. Dr. Brém, absolute pleasure having you on the program today.

Dr. Brém:
Same here, thanks again.

Announcer:
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