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On the Frontlines of CLL: First-Line Treatment & Long-Term Outcomes

Dr. Sands:
This is *Project Oncology* on ReachMD. I'm Dr. Jacob Sands. And joining me to review frontline treatments for chronic lymphocytic leukemia, or CLL for short, and emerging data on long-term outcomes is Dr. Bruce Cheson, a Scientific Advisor at the Lymphoma Research Foundation. Dr. Cheson, welcome to the program.

Dr. Cheson:
Thank you. It's good to be here.

Dr. Sands:
So starting off with some background, can you tell us about frontline treatments for CLL that are currently available?

Dr. Cheson:
To put this into historical perspective back in the 60s, we were just using drugs like chlorambucil and CVP and CHOP for the treatment of CLL. That was the first phase. In the 90s, we had the next phase which was a battle between a variety of purine analogs, which fludarabine emerged as the victor. The third phase in the treatment of CLL history was the introduction of rituximab, the anti-CD20 monoclonal antibody, and then came other CD20s, particularly obinutuzumab, which has emerged as probably a superior anti-CD20 for CLL.

We are now in the fourth phase. This is characterized by a large number of targeted and immunotherapeutic agents. The first of these involve the PI-3 kinase and PTK or proton-tyrosine kinase inhibitors. And we have several of these in each class that are now currently available. The next drug that became available was the PCL-2 inhibitor, venetoclax. And once these showed promise in the relapse and refractory setting, they were rapidly brought to the frontline. So patients with chronic lymphocytic leukemia today have a variety of treatment options as their initial therapy.

Ibrutinib, the BTK inhibitor alone or with rituximab is one of these. Another is a second generation BTK inhibitor, acalabrutinib, which is used either as a single agent, or in combination with obinutuzumab. Those two therapies are currently given indefinitely as long as the patient responds, and as long as the regimens are tolerable. On the other hand, we have a combination venetoclax and obinutuzumab, which is a time-limited therapy lasting a year.

So these are three of the most promising initial therapies for CLL. Now chlorambucil-based approaches and fludarabine, Cytoxan, and rituximab approaches are also used, but they are becoming just a part of history, as patients now have the opportunity to be treated with targeted chemo-free therapies.

Dr. Sands:
It is exciting to hear a lot of new drugs within that list that you're, providing. So with that overview in mind, let's focus on two different approaches. There's sequencing where one and then a progression another and then combination therapies. Can you describe a little bit about those two approaches and contrast and compare them?

Dr. Cheson:
Sure. Once one has more than one effective agent, the natural tendency is to put the two or more together to combine them. And whether these combinations are better than a single agent followed by another single agent remains a controversial and unknown factor in the treatment of CLL.

For example, ibrutinib was the first single agent to be approved as frontline therapy in the new era. When patients fail CLL therapy with

ibrutinib, they would go on particularly to venetoclax-based regimens. But given that these two are so highly effective as single agents, they have been put together. And the results are very promising. But we don't know whether responding to one agent for a period of years which you may get out of ibrutinib single agent followed by venetoclax-based therapy for another series of years is better than giving the two drugs concurrently.

And now that we have an anti-CD20 such as obinutuzumab, there are studies looking at the triplet of a BTK inhibitor such as ibrutinib with venetoclax with obinutuzumab.

All these combinations are very exciting. But the question is, what happens after a patient progresses on a regimen like that? We currently have a limited menu of treatments to follow. These include the PI-3 kinase inhibitors, and CAR T-cell therapy.

So there are a lot of studies which are combining agents. But whether that approach is superior to the sequence is unclear. It's very exciting. The response rates, the complete response rates the rate of undetectable minimal residual disease, or MRD, those are very high and exciting. But they're also very expensive.

And as I said, we don't have a long menu to treat patients following that sort of regimen. So it's an unanswered question. But I think given the enthusiasm that the CLL field has for such combinations, it's going to be hard not to use them as part of frontline therapy for CLL.

Dr. Sands:
Okay, so you've discussed sequencing versus combination kind of in general, but let's say you have someone sitting in front of you, the patient in front of you what is the discussion you have for that individual and how do you go through the different treatment options to those patients?

Dr. Cheson:
That's a very good question. There are three primary treatment options that we discuss. You can take FCR and chlorambucil and the other chemoimmunotherapy regimens and push them out of the way, because the targeted agents in randomized studies are superior.

So the three options are ibrutinib alone or with a CT20, acalabrutinib alone or with obinutuzumab, or venetoclax and obinutuzumab. Now, in general, my preferred regimen is venetoclax/obinutuzumab for a number of reasons. Number one, it's very effective. Number two, it has a high likelihood of eradicating detectable minimal residual disease. And number three, it is time limited, it's one year. The other two, for a variety of reasons you may not want to use venetoclax/obinutuzumab, for example, in patients with 17p deletion, who seem to do better with a BTK-based regimen.

Now ibrutinib totally changed the world of CLL. It was the first targeted drug to first show efficacy in the relapse setting and then to be approved in the frontline setting. But there are issues with tolerability. And acalabrutinib is a second generation BTK inhibitor, is comparably effective, as shown in randomized study and appears to be better tolerated. So if the patient wasn't a good candidate for venetoclax/obinutuzumab, my therapy of choice would be currently acalabrutinib and obinutuzumab because it appears to be slightly better. Although acalabrutinib as a single agent is also a viable option.

There are other BTK inhibitors coming down the pike such as zanubrutinib, which again compared to ibrutinib, appears to be similarly efficacious and better tolerated.

So in general, those are the options and you pick them, right now, based on your familiarity with them, and a variety of patient preference features. Does the patient want to be on a pill indefinitely? Or do they want a regimen that's one year but involves a number of intravenous infusions.

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. Bruce Cheson about different treatment approaches to chronic lymphocytic leukemia.

So, Dr. Cheson, let's switch gears a little bit and look at the data and long-term outcomes from trials like MURANO and CLL14. What can you tell us about this emerging data?

Dr. Cheson:
Well, the MURANO study is actually a study conducted in relapsed refractory CLL. And in this study, patients were first treated with venetoclax followed by rituximab and venetoclax, and compared directly in a randomized fashion with bendamustine/rituximab. And recently, we've seen data beyond four years with this comparison. And what these data show is a persistence of a superiority in progression-free survival, overall survival, likelihood of becoming undetectable MRD.

Now a number of other important observations have been made in this study. For example, the kinetics with which MRD becomes

detectable may be an important prognostic factor. That's been learned from long-term follow-up with the study. And another interesting observation is, if you take the patients, around two-thirds of them that become undetectable, and you follow them over time, it takes more than a year and a half for the MRD to become detectable again. And about two years after that, for patients to require retreatment. So just becoming detectable is not an indication for therapy, because you can wait for years, and the patient now can live a relatively normal life. And in the meantime, newer and more exciting therapies are in development. So the MURANO was the first regimen in the relapse setting to demonstrate these really exciting findings.

Dr. Sands:
And how might this long-term follow-up data impact our treatment perspectives and outlooks?

Dr. Cheson:
Well, what we know now is that patients receiving venetoclax-based therapy for one year have more than 80% chance of being out four years and beyond without progression. And those observations are stunning. It means that patients short-term therapy, long-term benefit. And once they progress at that point years down the road, they can be retreated successfully, or they have the opportunity to receive other therapies such as BTK-based therapy, PI3K-based therapy, or even CAR T-cell therapy, should they need one of those approaches.

This gives patients optimism that with a non-chemotherapeutic regimen, no chemotherapy, they may have years of good quality of life, on no treatment whatsoever. And this will eventually likely improve their outcome. So it’s a major breakthrough, both from the CLL doctor perspective, but more importantly, from the patient's perspective.

Dr. Sands:
It is exciting to hear so much going on in CLL treatments. Before we close, I just ask you, do you have any final thoughts or advice on how we can better treat patients with CLL in the frontline setting, all really particularly with attention to these long-term outcomes?

Dr. Cheson:
Well, we are now in a totally new world in the treatment of CLL patients, particularly in the frontline. We have several non-chemotherapy-based approaches, which have been shown in randomized trials to be superior to chemoimmunotherapy. But what we need to do is first to answer the question, which patients are best suited for which regimen. And at this point in time, we have a few clues, like 17p deletion probably better dealt with a BTK-based regimen. But there are other molecular and genetic findings that may be better suited to telling us which patients should get this single drug, this combination of drugs, or the sequence of drugs. So we need to learn more about the disease and how to treat it.

Dr. Sands:
Well, there certainly is a lot to discuss for CLL, and it is always wonderful to hear about progress, uh, but that is what we have time for today. I do want to thank my guest, Dr. Bruce Cheson, for joining me to discuss the available treatment options and long-term impact for CLL. Dr. Cheson, absolutely wonderful having you on the program today.

Dr. Cheson:
Thank you. It's been great being here.