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The CLL Landscape: A Look at Current and Future Therapies

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

Dr. Russell:

This is *Project Oncology* on ReachMD. I'm Dr. John Russell. Here with me today to explore the current treatment landscape for chronic lymphocytic leukemia, or CLL for short, is Dr. Andrew Lipsky. Dr. Lipsky is Assistant Professor of Medicine at Columbia University Medical Center in New York City. Dr. Lipsky, welcome to the program.

Dr. Lipsky:

Happy to be with you today.

Dr. Russell:

So before we talk about available treatment options, can you tell us about the impact CLL can have on our patients if it's left untreated?

Dr. Lipsky:
Absolutely. So I think in answering that question, it's really important to differentiate CLL from other malignancies in the sense that many of our patients, upon diagnosis, don't need treatment right away. And so at least a third of patients will be placed on watch and wait indefinitely, and maybe an additional third will be placed on watch and wait initially and then subsequently need treatment. And so thinking about the ways that CLL can impact your life, just in virtue of having the diagnosis, I think that's important for any CLL physician.

So for a CLL patient that's newly diagnosed, learning to live with a cancer without treating that cancer—because we have several studies showing that early treatment initiation before you truly meet iwCLL treatment criteria—is invaluable in terms of the toxicity profile trade off. Just establishing a therapeutic relationship with the patient to allow them to understand CLL, begin to understand what the future might look like in terms of therapeutic modalities once they have a true treatment indication, and really establishing that therapeutic relationship with your patient can help to alleviate some of the anxiety that's associated with a new cancer diagnosis in where you're not initially going to start treatment right away. I think that's super important.

And then of course, as the patient continues on watchful waiting with active surveillance, we think about the many ways that this disease can impact their life as it begins to approach needing treatment. So we think about patients with infections, and we think about patients and their need for dermatologic screening; the risk of skin cancer is elevated in this particular patient population. We think about the importance of keeping up to date with vaccination strategies. And then, as we start to see momentum of the disease growth itself, we think about the iwCLL treatment guidelines and indications for treatment. So, of course, CLL can involve the bone marrow and certainly result in cytopenias, be that a patient develops anemia or a thrombocytopenia secondary to the CLL, which require treatment, and the other ways in which the disease can impact their life that are not purely based on any counts.

Dr. Russell:
And when you start making that move from watchful waiting to entering the treatment landscape, what are the therapeutic approaches that are currently available?

Dr. Lipsky:
So in the frontline setting for CLL, there are really two paradigmatic mainstays of therapy. The first approach is indefinite therapy with a BTK inhibitor. So in that approach, the patient is given a prescription for a BTK inhibitor and takes one of the three approved drugs in the

frontline setting—that's ibrutinib, acalabrutinib, or zanubrutinib—indefinitely until progression of disease.

The other strategy is not indefinite in nature but is also excellent in terms of the outcomes for our patients, and that's a time-limited therapeutic approach with venetoclax plus obinutuzumab. In this treatment paradigm, we initiate therapy with obinutuzumab, an infusional anti-CD20 antibody, to begin debulking the disease, and then the patient starts a fixed schedule of venetoclax ramp-up, starting at 20 milligrams and ramping up to 400 milligrams. And the patient then completes up to a year of therapy and stops that therapy and begins again a treatment-free interval in which the disease is monitored.

Dr. Russell:
So, doctor, what are some of the treatment guidelines you turn to, to kind of help you make some of these decisions? And how do they line up with some of the things you just talked about?

Dr. Lipsky:
Sure. So there are treatment guidelines available from organizations like the NCCN. There are also specific indications for treatment from the International Workshop on CLL, or the iwCLL treatment guidelines. And if you look at those guidelines, and I'll start with NCCN, what you see is that for upfront patients, either a time-limited strategy with venetoclax and obinutuzumab or an indefinite strategy with a BTK inhibitor is acceptable for frontline patients.

The NCCN goes a bit further to highlight when choosing an indefinite treatment strategy that they have a preference for second-generation BTK inhibitors. So that's acalabrutinib and zanubrutinib over the first-generation BTK inhibitor ibrutinib. And that is really an extrapolation based upon studies comparing the second-generation BTK inhibitors to ibrutinib in the relapsed/refractory setting. And in that setting, they clearly demonstrate a better overall safety profile. And so the NCCN, for that reason, has recommended as a more preferred agent either zanubrutinib or acalabrutinib in the frontline setting.

Dr. Russell:
So, doctor, on top of all these guidelines, are there some newer research that's come out that has helped you modify how you apply some of these therapies?

Dr. Lipsky:
For me, the most interesting study that was presented recently at ASH that bared on frontline CLL was the ELEVATE TN study. So this was a study of acalabrutinib, a BTK inhibitor, that was administered two ways. It was either administered as a monotherapy BID until progression or toxicity, or it was administered in combination with obinutuzumab. And here, the addition of an anti-CD20 therapy was something we were all very interested in seeing as to whether that would have an impact on progression-free survival and in which subgroups that may make a difference.

So now we have the 6-year follow-up data of acalabrutinib plus obinutuzumab or acalabrutinib monotherapy compared with the control arm of chlorambucil plus obinutuzumab. And I think one of the very interesting things about this study is that we did see the progression-free survival being most advantageous for the combination of acalabrutinib and obinutuzumab. So at 72 months of follow-up, the PFS for that double combo was 78 percent, versus the acalabrutinib monotherapy was 62 percent. And of course, the control arm—the chlorambucil/obinutuzumab—had a far inferior PFS of 17 percent.

So really, it was very interesting for us to see that obinutuzumab, when added, does appear to translate into some progression-free survival benefit. Now, we saw subgroup analysis from that study suggesting that the patients with TP53 aberrations, the high-risk CLL group, didn't actually benefit from the addition of anti-CD20 therapy to acalabrutinib.

Dr. Russell:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. John Russell, and I'm speaking with Dr. Andrew Lipsky about the CLL treatment landscape. Dr. Lipsky, what data is available for treatment paradigms for the patient who has relapsing/remitting CLL?

Dr. Lipsky:
That's a great question. I think it's really important to highlight some new data that was presented at this year's ASH meeting, which bears specifically on the approval of a new drug for CLL in the relapsed/refractory setting, and that's pirtobrutinib.

So this was the BRUIN study, which was presented. This was a follow-up of a phase 1 to 2 study of several patients, over 300 patients with CLL, who had received prior BTK inhibitors for the majority of this patient study population. And we saw data for both patients who had been exposed to the BTK and BCL-2 inhibitors, as well as for the patients who were just exposed to the BTK inhibitors and who were BCL-2 naïve. And in both of these patient populations, we saw that pirtobrutinib was highly efficacious from the standpoint of progression-free survival. And so if you were relapsed/refractory and you had received a BCL-2 inhibitor, the median progression-free

survival was 15.9 months. And if you had not received a BCL-2 inhibitor, you're BCL-2 naïve, the median progression-free survival for that subgroup was 23 months. And again, that was a subgroup analysis of the original data we saw, where in all patients receiving pirtobrutinib on this study—again, a highly pretreated patient population—the overall median progression-free survival was 19.4 months.

And so this particular drug has now been approved for relapsed/refractory CLL in patients who have been exposed to both a BTK inhibitor and a BCL-2 antagonist. And I think that's a tremendous addition to our armamentarium for treating patients with relapsed/refractory CLL.

Dr. Russell:
So we've talked a lot about the current treatment landscape. What do you envision as the future of CLL treatment?

Dr. Lipsky:
So we do have excellent options for CLL patients with relapsed/refractory disease that are currently in clinical and preclinical development. I'll talk about two classes or mechanisms of actions of these particular drugs.

The first that I'm sort of most excited about in the short term is the BTK degraders. So this is another way of targeting the Bruton's tyrosine kinase protein instead of covalently binding to the molecule or noncovalently binding to the molecule. We use the cell's own molecular machinery—the proteasome, the garbage disposal of the cell—and target the BTK protein for degradation directly by the cell itself. This has clinical promise, and indeed, we've seen the preclinical data and some of the clinical data suggesting that this type of approach would overcome any of the resistance mutations that we see, be that from first-generation, second-generation, or even third-generation BTK inhibitors. And so I think it's very exciting to continue to follow that space and look as we continue to see more clinical data from the various compounds that are currently in clinical trials for BTK degradation.

The second class of agents that I'll talk about is the bispecifics. These are bispecific antibodies. Essentially what they do is they bring the CLL cell in contact with a T cell, so they function as a form of immunotherapy. In this regard, these agents have been approved in several other diseases, including diffuse large B cell lymphoma and multiple myeloma. And the data for CLL has been presented in the EPCOR CLL study. And we really did see in a very heavily pretreated group of patients a high overall response rate, showing that this particular mechanism, the CD20/CD3 bispecific antibody, really holds great promise in continuing to achieve excellent responses and durable responses in patients with heavily pretreated relapsed/refractory CLL.

Dr. Russell:
Thanks for sharing all that great information. And that brings us to the end of today's program. I want to thank my guest, Dr. Andrew Lipsky, for joining me to discuss the latest guidelines, evidence, and treatment options for chronic lymphocytic leukemia. Dr. Lipsky, it was great having you on the program today.

Dr. Lipsky:
Pleasure to be here.

Announcer:
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