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State of the Union on CLL: Evolving Diagnostic Biomarkers & Outcomes

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

Dr. Caudle:
Welcome to Project Oncology on ReachMD. I'm your host Dr. Jennifer Caudle, and joining me to talk about diagnostic biomarkers and outcome measures for patients with chronic lymphocytic leukemia is Dr. Lindsey Roeker, a hematologist and medical oncologist with expertise in leukemia at Memorial Sloan Kettering Cancer Center. Dr. Roeker, welcome to the program.

Dr. Roeker:
Thanks so much for having me.

Dr. Caudle:
So Dr. Roeker, let's start by level setting our current understanding of diagnostic biomarkers for chronic lymphocytic leukemia, or CLL for short. Can you give us an overview of how these biomarkers are derived and what they indicate?

Dr. Roeker:
Absolutely. So, when I think about making the diagnosis of CLL, and really figuring out what a patient's prognosis is, there are a few tests that I perform routinely. So, the first one is flow cytometry. And what that is, is really a cell-sorting test. So, I describe it as putting all of the white blood cells into buckets. So, you have buckets of normal-looking cells. And then you have your bucket of abnormal-looking cells. And in CLL, those are cells that are both CD-5 and CD-23 positive. And once that bucket is identified, then you can quantify those cells. So, any person who has greater than 5,000 cells per microliter of clonal B cells with that phenotype is diagnosed with CLL. And that's the first test that we use to really establish a diagnosis.

And then there are additional tests that we can use for prognosis. So, the tests that I routinely perform at the time of diagnosis are cytogenetics, which includes FISH and either SNP array or karyotype depending on the lab and their capabilities IGHV mutational testing, and then next generation sequencing. And I routinely perform these for patients at the time of diagnosis because they really do give prognostic information that patients can use and you can use to determine, you know, how often you're going to monitor and kind of what to expect from the disease course. Though, even if they're not performed at diagnosis, certainly these are tests that are important to perform before a patient starts therapy. So, for all patients, that pre-treatment testing is really an important piece.

And breaking them down one by one, so, the first piece is cytogenetic testing, which includes FISH and SNP array or karyotype. And there are specific mutations we're looking for. So there are poor prognostic factors for instance, deletion of 17p or deletion of 11q. They're kind of these intermediate-risk groups, which are trisomy 12. And then favorable risk, which is deletion of 13q. Further, you can use karyotype, and that's really what's been validated in looking at a complex karyotype, which historically has been defined as three or more genetic abnormalities by karyotype, though there is some indication that five or more genetic abnormalities carries even a worse prognosis. And that complex karyotype just gives a sense of or genomic instability that really leads to a higher risk disease. So that's your cytogenetic testing. Then there's IGHV mutational testing.

When I'm talking to patients about this test, I basically describe that IgG mutational testing tells you how grown up cells were when they went from normal B-cells into CLL cells. If you have an unmutated IGHV, that's like a child. So that was a cell that was unmutated, before the B-cell was really matured. And those tend to behave less well. So they tend to be a little bit more aggressive and don't respond quite as favorably to therapy. Whereas mutated IGHV are more like adult cells, they've gone through that maturation process,

tend to be a little more indolent, and respond more favorably to treatment.

And then last is next generation sequencing. So, the mutation that we really focus on is TP53. Since TP53 mutations have been associated with less favorable prognosis overall, but NOTCH1 mutations can also be helpful in kind of assessing risk for transformation. And there are other mutations that are kind of under exploration. Our typical testing is done through a clinical trial and it's 400 different cancer-related genes. But even if that like large panel isn't available definitely next generation sequencing for TP53 is an important piece.

Dr. Caudle:
Excellent, thank you. And, you know, how do these biomarkers influence treatment rationales for patients with CLL?

Dr. Roeker:
So the major testing piece that I think is important in decision-making is your IGHV mutational status. The reason is, we know that there's still a subset of patients who are young and fit, who have mutated IGHV, that derive prolonged benefit from FCR chemotherapy. So in general, CLL is a disease that over the last seven years has undergone radical transformation in terms of treatment modality, going from a disease that was primarily managed with chemoimmunotherapy to one for which we have these targeted agents that work really, really well.

However, there's still this subset of patients who were always hesitant to use the word cure with a chronic illness. But there is a subset of patients with IGHV mutated disease who do not have TP53 mutations or deletion of 17p, who seem to derive long-term benefit with FCR. And for those patients, I still talk about the possibility of FCR as a frontline therapy. For all other patients, anybody with an unmutated IGHV status or who has a TP53 aberration, either deletion of 17p or TP53 mutation we're kind of in the novel agent realm, and I talk to them about their treatment options within that category.

Dr. Caudle:
Excellent. Now, if we turn our attention to outcome measures, what endpoints do the current guidelines recommend for measuring the impact of treatment?

Dr. Roeker:
This is a fabulous question. So in general, our response assessments are still based on kind of basic tests. So CBC, we look at hemoglobin, platelets, and lymphocyte count. And then also spleen size and lymph node size. So clinical response is still based on kind of these basic measures.

There are more tests that we're still understanding how to use in clinical practice. And right now, they don't have a huge role in routine clinical practice, specifically MRD status or minimal residual disease. And this can be tested either with flow cytometry or with next generation sequencing through identification of the IgG mutational signature. And that MRD test is one that is used a lot in clinical trials, and we're kind of learning how they should be incorporated into routine clinical practice. But for right now, response assessments really are based on kind of those standard clinical responses as defined by iwCLL, which is sort of like the consensus guidelines for how to judge response to therapy.

Dr. Caudle:
For those of you who are just tuning in, you're listening to *Project Oncology* on ReachMD. I'm your host, Dr. Jennifer Caudle, and I'm speaking with Dr. Lindsey Roeker about biomarkers, endpoints, and outcomes for patients with chronic lymphocytic leukemia.

So Dr. Roeker, let's keep exploring outcome measures for just another moment. What kind of role does undetectable minimal residual disease play as an endpoint for patients with CLL?

Dr. Roeker:
Fabulous question. So we know that from the chemoimmunotherapy literature there is a link between MRD status and progression-free survival. And then from the MURANO data, which was the study that looked at venetoclax and rituximab in patients with relapsed and refractory CLL, the MRD status at the end of therapy, so venetoclax/rituximab is a fixed two-year duration therapy, at the end of treatment, they checked MRD status. And we see that progression-free survival is linked to how deeply patients responded. So those who achieved an undetectable MRD status enjoy a superior progression-free survival compared to those with either low-level MRD or high-level MRD.

So we know that MRD is linked at least in venetoclax-based therapy and chemoimmunotherapy to progression-free survival. And the role for MRD as an endpoint in guiding treatment duration is really being explored. So there are combination studies, specifically novel-novel combination. So studies that are looking at BTK inhibitors along with venetoclax, or some sort of B-cell receptor inhibitor combination that are using MRD as an endpoint. So a goal that, once it's achieved, we can stop therapy. And that's a strategy that really

is still being explored in the clinical trial setting. So in routine clinical practice, that isn't being used, but certainly as this field evolves, I think it will play an increasing role in deciding how long patients really do need therapy as sort of an individualized approach to treatment.

It's also important to remember that, BTK inhibitors are incredibly effective for CLL therapy, but don't achieve the same depth of response as venetoclax-based therapy or chemoimmunotherapy. And there are patients who really have prolonged periods of disease control despite either achieving a partial response or stable disease. And in those therapies, it really doesn't seem that depth of response is as quite as important or at least we're still figuring that piece out. And we know that there are patients who can have prolonged response despite not achieving MRD. So, I think MRD isn't the entire the entire story but is going to play a role indecision-making probably in the future.

Dr. Caudle:
Okay, and, you know, now if we bring these two components together, how do biomarkers and outcome measures play a role in shared decision-making practices?

Dr. Roeker:
So, when I'm talking to patients about their therapy in the frontline setting, the first thing I look at is really, am I going to even talk to them about chemoimmunotherapy. And I'm really using IGHV mutational status, TP53 aberration status to guide that decision.

So if FCR is part of the discussion, that's based on biomarkers. If they have not that ideal FCR candidate kind of characteristic, then I'm talking about novel agents. And when I'm talking to patients about novel agents, we don't have any head-to-head data, looking at BTK inhibitor-based therapy versus venetoclax/obinutuzumab in the frontline setting. So in the absence of comparative data, I really do use shared decision-making to determine what that frontline approach should be.

So I talk to patients about continuous therapy with BTK inhibitors versus time-limited therapy with venetoclax/obinutuzumab. I talked about the need for close monitoring in the upfront part of the regimen. So certainly venetoclax/obinutuzumab requires more monitoring up front than BTK inhibitor. And there's kind of a trade-off there. So I talk to patients about both approaches and use really their preferences to guide our frontline decision-making.

In outside of a clinical trial setting right now, I really don't use MRD to guide treatment decision-making, though I do check it at the end of fixed duration therapies to help patients understand what to expect. So, I use it more prognostically than as a decision-making tool.

Dr. Caudle:
Understood. And before we close, Dr. Roeker, do you have any final takeaways for our oncologists to keep in mind?

Dr. Roeker:
Absolutely. So, I think it's good to remember that prognostic biomarkers are an important part of the initial workup for CLL, either at the time of diagnosis, but definitely before patients are starting therapy. So, there's kind of your FCR ideal candidate who might achieve really long-term responses with FCR, that IGHV mutated patient without a TP53 aberration. And knowing all of those pieces of data are really important for that up-front decision making.

And then I think it's useful to know that MRD is kind of coming in the coming years as a marker that we're probably going to be using for clinical decision-making, but for right now, isn't part of the routine clinical decision-making as we're using either fixed duration or continuous therapies.

Dr. Caudle:
Excellent. Well, with those final takeaways in mind, I'd like to thank my guest, Dr. Lindsey Roeker, for joining me to discuss chronic lymphocytic leukemia and to share her thoughts on diagnostic biomarkers and outcome measures. Dr. Roeker, it was wonderful having you on the program today.

Dr. Roeker:
Thank you so much, really appreciate it.

Announcer:
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