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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Tailoring CLL Treatment Strategies & Improving Outcomes

Announcer:
You're listening to *Project Oncology* on ReachMD, sponsored by Lilly. Here's your host, Dr. Jacob Sands.

Dr. Sands:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands. And joining me to dive into key factors guiding treatment decisions for patients with chronic lymphocytic leukemia is Dr. Nicole Lamanna, a Hematologist Oncologist at Columbia University Medical Center with research interests in lymphoid leukemia, specifically chronic lymphocytic leukemia, or CLL. Dr. Lamanna, welcome to the program.

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

Dr. Sands:
Dr. Lamanna, we have a lot to cover, so let's dive right in. What are some specific disease-related factors you use to guide your treatment approach for patients with CLL?

Dr. Lamanna:
Given that this is a chronic leukemia, and it's very heterogeneous, in other words, there are patients with what we call good risk features to their disease. And usually those are the patients that can be monitored for a long period of time. But there are patients' disease biology that sometimes has more aggressive features. So, it's always important, if not at diagnosis, but certainly prior to initiating any type of chemotherapy, or I should say any therapy, not necessarily chemotherapy, but any therapy, that we're going to try to test for their disease-related biology. So they're looking at their FISH or cytogenetics. Or we're looking at chromosomal abnormalities that are associated with their disease because we want to know if they're good risk or not, patients who, let's say, have a deletion 17p or a p53 mutation are considered high risk. And so we would absolutely, if needing therapy, would not recommend chemoimmunotherapy. So that's an important part that we would want to know about prior to initiating any treatment. If they have a complex karyotype, so multiple chromosomal abnormalities usually greater than three, then also they're more high risk. And again, we would not recommend chemoimmunotherapy but more targeted treatments for that. And then we want to know the molecular testing, their IgHV, mutational status. Are they mutated versus not mutated? The mutated folks are more favorable and have more treatment options. If you're unmutated, less favorable. Again, we would not give chemoimmunotherapy, we would recommend some of these novel targeted treatments. And so it's really important to have some of this testing.

Dr. Sands:
Now that we've covered disease-related factors, what are some patient-specific characteristics you typically consider?

Dr. Lamanna:
This is very akin to probably what we do with many of our patients. Of course, comorbidities are always a factor in deciding what particular treatment options might be better for one patient to another. The good news about CLL is that there are so many treatment options available that you can kind of hone things a little bit more specifically.

So for example, as we talked about earlier, disease characteristics are important. But then because we have novel targeted agents, and I'm specifically talking about BTK inhibitors, such as ibrutinib and acalabrutinib, and then we have BCL2 inhibitors, such as venetoclax, we have lots of good options, and then we can look at patient's comorbidities. So if somebody has a severe coronary artery disease, hard to control hypertension, they're on anticoagulation, perhaps for atrial fibrillation, or for another reason, then we might choose accordingly different treatment options, because of those disease characteristics, we might favor a different drug. Because of their

comorbidities. We might look at either a second generation BTK inhibitor or venetoclax-based therapy. If they have poor kidney function, then we might decide to avoid a drug like venetoclax, which we know can have tumor lysis, and we have to monitor their kidney function very closely, and favor a different option such as BTK inhibitors.

So comorbidities absolutely play a role in choosing the various options that we have for CLL, which is great because we have them. Before we didn't have this many options. In addition, oftentimes a patient preference will also play a role now. Again, with all these options, we will now talk about what we call chronic continuous therapy. So taking a medicine every day, such as a BTK inhibitor that they can take daily, like they do maybe other medicines for their other medical problems. And they take that until until if they're having a side effect from the therapy that we can ameliorate and have to discontinue, or until if they have disease progression, in other words that the drug isn't working anymore. When I say chronic continuous therapy, that's definitely the BTK inhibitors. So patient preference, chronic continuous therapy versus time-limited therapy also plays a factor in addition to their comorbidities.

Dr. Sands:
So you've covered some specific disease-related factors, as well as patient-specific characteristics. But what are some of the qualities of the therapies themselves that we should keep in mind? You've touched on this a bit as far as the scheduling, but are there any other aspects?

Dr. Lamanna:
Yeah, absolutely. So I mean, just to reiterate, each of these medications and others, along with any disease that we treat, clearly there are nuances to how to finesse some of these treatments. And BTK inhibitors in particular there are obviously some cardiac issues that we need to monitor for and high blood pressure atrial fibrillation, so they can cause cardiac arrhythmias, and so we counsel patients about that. But typically, an easier medication in general to initiate somebody with CLL on because it doesn't require a lot of monitoring from a blood count perspective. It's something that can be done easily as an outpatient without a lot of concern for tumor lysis syndrome. And so we usually educate patients about the potential side effects of these therapies. But definitely a therapy that's easy to initiate.

Venetoclax-based therapies, even though they're time limited and it's appealing in that way, certainly we have to monitor patients more closely. And so for somebody with CLL, if they have high-risk disease, so bulky lymph nodes or organomegaly or a very elevated white blood cell count, we know they're going to be at risk for tumor lysis syndrome. And when we start a drug like venetoclax, they require what they call a dose ramp-up so that they start on one dose on week one, and each week, their dose is escalated until they hit a target dose. And so it requires a five-week dose ramp-up. So for patients who have bulky lymph nodes or organomegaly or a high white count, believe it or not, they're considered high risk for tumor lysis. Those are the patients that, believe it or not, require a hospitalization to initiate the dose ramp-up so that we can monitor their kidney function and their electrolytes very closely give them I.V. hydration give them allopurinol or other anti-hyperuricemic agents such as rasburicase if it's needed or forced diuresis with Lasix. So a high-risk disease, those patients require hospitalization.

Low-risk disease, you can do it as an outpatient, but they still require a lot of electrolyte and lab work monitoring in the clinic. So for patients, sometimes this may not be very convenient. And that's why patient preference might play a role into sometimes the options that a patient chooses, because they'll need to come in weekly. Usually, we'll bring our patients actually day one, day two, to monitor their blood work in the clinic. And so it's not difficult but it requires monitoring and putting in the time and so, depending upon what the patient is able to do, sometimes that can be difficult because they'll need to do that weekly for five weeks.

So time-limited therapy, absolutely more work upfront, as a commitment to make sure that the patient is ensured safety so we can monitor their kidney function and electrolytes for monitoring for tumor lysis. BTK inhibitor is easier but chronic continuous therapy. And like many chronic continuous therapies, of course, sometimes you can have toxicities that occur later or chronically. And so then drug adherence and compliance can be an issue if they get mild but nagging side effects, sometimes diarrhea or other issues, sometimes patients like to come off for those reasons when they're taking a chronic daily medicine. But certainly less monitoring needed on the clinic and/or on the clinical end because there's not tumor lysis. And so, we look at the toxicities and we also pair that with disease characteristics, patient preference, and all the things we talked about earlier when we talk about how to choose drugs also based on some of the toxicities or needed issues that have to be monitored depending upon the drug.

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. Nicole Lamanna about strategies for tailoring chronic lymphocytic leukemia treatment.

So Dr. Lamanna, now that we've covered all the various factors needed to consider, let's take a step back and look at the bigger picture. If we tailor our approach based on these considerations, what kind of impact can that have on patient outcomes?

Dr. Lamanna:

We've been really fortunate with CLL over the past decade. When we think about where we've come, if you look at the treatments that have been, evolved for CLL, we started in the 1950s with drugs like, chlorambucil and cyclophosphamide. So the oral alkylating agents. We moved into the era of purine analogue therapies, so much more aggressive chemotherapy that developed in the 1980s. And then we added the monoclonal antibodies such as rituximab in the late 1990s. And combined those drugs together for chemoimmunotherapy, more toxic aggressive therapies. Fast forward to the last decade, and we have novel targeted therapies on the B-cell receptor pathway. This is the BTK inhibitors, the BCL2 inhibitor, venetoclax. And so we really know these targeted therapies, much less toxic than chemoimmunotherapy that we gave decades ago.

But in addition, they've absolutely improved both the progression-free survival and overall survival of CLL patients, even patients with high-risk disease such as 17p or a p53. mutation. When we gave those folks chemoimmunotherapy, their life expectancy was very short. As a chronic leukemia, high-risk disease was very poor. Patients actually usually died within a few years. Now we have novel targeted therapies for these individuals. And already, their survival has dramatically improved. And people are living years, even with the worst or highest risk features to their disease. And then they can go actually from one novel targeted agent to another. So survival in CLL continues to improve with these novel targeted therapies.

So there's lots of stuff going on in the world of CLL that's very exciting. And as I said, we've already seen this dramatic improvement in survival in response to patients with CLL based on some of these novel targeted therapies. So the futureis very bright. But we continue, to look for new agents that are curative. So we still call CLL a chronic leukemia, but certainly we're doing better and better and patients A: have better quality of life with some of these therapies compared to our chemoimmunotherapy era, and certainly are living longer. So hopefully, we'll continue to improve upon the success that we've had in the last decade.

Dr. Sands:
Before we close, do you have any advice for fellow colleagues to help them guide their treatment decisions?

Dr. Lamanna:
It's really important to make sure that the patients are tested with their chromosomal abnormality. So FISH testing and their IgVH molecular testing. Because, we're now moving away from chemoimmunotherapy in general, but I know that a lot of physicians are very comfortable with chemoimmunotherapy. However, we should absolutely in patients with high-risk disease not be administering chemoimmunotherapy for patients with 17p, p53, complex karyotype, or those who are unmutated. So novel agents are absolutely recommended for those individuals if you're still giving chemoimmunotherapy. So it's important to test for that.

And any questions or concerns about how to manage the finer toxicities of these agents reaching out to colleagues who administer some of these drugs like the venetoclax, which can be a little bit tricky giving patients tumor lysis or how to manage individuals who are high risk or require hospitalization, folks can absolutely reach out.

Dr. Sands:
It's very helpful. It's very exciting to see how much has happened in CLL. And with that in mind, I would like to thank you for joining us to explore key factors guiding treatment decisions for patients with chronic lymphocytic leukemia. It was a lot of fun having you, Dr. Lamanna, on the program.

Dr. Lamanna:
Thank you very much.

Announcer:
This program was sponsored by Lilly. To revisit any part of this discussion and to access other episodes inthis series, visit ReachMD.com/projectoncology where you can Be Part of the Knowledge. Thanks for listening.