LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Empowering Lives: Advancements in Chronic Lymphocytic Leukemia'

Description:

Join us as we sit down with Dr. Deborah Stephens from the University of Utah, as we discover the latest breakthroughs in treating chronic lymphocytic leukemia (CLL). We also gain valuable insights into enhancing patient's quality of life.

In this episode, Dr. Stephens emphasizes the importance of effective communication with your healthcare team, unveiling strategies that not only optimize disease management, but also minimize the impact of side effects. Your path to empowered long-term care with CLL begins here.

Transcript:

Elissa: Welcome to *The Bloodline with LLS*. I'm Elissa.

Lizette: And I'm Lizette. Thank you so much for joining us on this episode.

Elissa: Today, we will be speaking to Dr. Deborah Stephens, a hematologist/oncologist and the Director of the Chronic Lymphocytic Leukemia, or CLL program, at Lineberger Comprehensive Cancer Center at the University of North Carolina. Her primary research interests include developing new targeted therapies for patients with CLL and lymphoma, studying resistance to current therapies, and developing supportive therapies for complications of CLL. Dr. Stephens is the principal investigator of multiple clinical trials. She has a deep commitment to improve the care of patients with CLL and lymphoma.

Welcome, Dr. Stephens.

Dr. Deborah Stephens: Thanks so much for having me today.

Elissa: Our episode today is on chronic lymphocytic leukemia, or CLL. We also hear the diagnosis small lymphocytic lymphoma, or SLL. Could you explain what these are?

Dr. Stephens: Sure, I'd be happy to. Chronic lymphocytic leukemia and small lymphocytic lymphoma, they are essentially cancers of white blood cells. So, when you think about your blood, you have three main solid components to it. You have red blood cells; those are the cells that help you to carry oxygen around. And if those are low, it's called anemia.

You also have platelets. Those are cells that help your blood to clot. And in the case that they're low, you might have issues of bleeding.

And then you have this whole other group of cells called white blood cells. The white blood cells are supposed to be there to be part of your immune system, help you fight off infections; and there's a specific kind of white blood cell called a lymphocyte, and this is where the cancer comes from. So, essentially, at some point during the development of this white blood cell called the lymphocyte, something mutates, and the cells start growing more than a normal cell would do. And normally blood cells, you make them, you use them, you recycle them; but these cells just don't die. So, basically, they grow faster than usual, and they don't die off like they should.

So, what happens is you get a collection of these cells either in your blood or sometimes in lymph nodes or organs like the spleen or liver, and they can cause symptoms that sometimes cause doctors to flag and diagnose with chronic lymphocytic leukemia.

What's interesting about small lymphocytic lymphoma, or SLL, I think it's a little bit of a confusing term for people because sometimes people say, "CLL or SLL," and CLL is called a leukemia, and SLL is called a lymphoma. And so, I don't really love the term SLL because I think it does make it a little bit more confusing for people.

But, really, the reason why there's a designation is it depends on where it comes in your body. Leukemia, if you break it down, means white blood cell in the blood. And so, if you have a lot of circulating white blood cells, and you have to have over 5,000 of those to meet the criteria to be officially called CLL, or chronic lymphocytic leukemia, if you just see a lot of these very same cells, they're exactly the same cells, but maybe they're concentrated in your lymph nodes or the spleen, then that is when it's called SLL. And so, you would have less than 5,000 of those cells circulating around in your blood.

I explain it to patients that it's like thinking about if you have a couch in your living room and you decide to move it to your basement, it is still the same couch; it's just in a different location. I think it does get really a little bit confusing for people. And when I talk to my patients, I generally just talk about CLL because all the treatments are the same.

The other thing that gets a little bit confusing is the staging system for CLL is different than the staging system for SLL.

Elissa: Oh!

Dr. Stephens: So, SLL is staged like non-Hodgkin lymphomas. It's pretty confusing because in non-Hodgkin lymphomas, if your bone marrow is involved, you're automatically Stage 4 disease. However, if you have SLL, you are always going to have involvement in the bone marrow because it's actually a leukemia. People come to me saying, "My doctor said I had Stage 4 cancer." And if they're staging with a non-Hodgkin lymphoma staging system, that's true; but they might actually have just a Stage 0 when we use the Rai staging system for CLL. There's a lot of things that make it confusing and so I generally stick with the term CLL.

Elissa: Yeah. And just the term, "Stage 4", can be very scary for patients, even though it means something different with lymphomas than it would be with a solid tumor.

Dr. Stephens: Hundred percent agree.

Lizette: Now, doctor, what are the common signs and symptoms of CLL and how is it usually diagnosed?

Dr. Stephens: The interesting part about CLL is, I would say the majority of patients actually have no symptoms, and they are diagnosed, they're completely asymptomatic. And so how do people find this? They're just getting a routine blood draw and their doctor notices that their white blood cell count is too high. And so, then the doctor would do some additional testing to look, what kind of white blood cells are higher? Are they abnormal cells? Do they look like CLL cells?

That's what's hard because people come in feeling completely fine. They're going for a well doctor check; they're going in to get surgery and the doctor just checks a blood count, and they find out that they have this type of cancer.

Alternatively, if people do have symptoms, it's usually enlargement of their lymph nodes or glands; and the easiest places to find those in your body are in your neck, under your arms, or in your groin. There's actually 500 to 700 lymph nodes in every adult, however, you can't feel all of those on the outside because most of them are tucked within in the abdomen or in the chest.

Sometimes you can have swelling. This is usually not painful. You get painful swelling of lymph nodes when you have an infection, usually. So, these are non-painful lymph nodes that are enlarged. These can go up and down in size a little bit too, so often it takes a little while to diagnose people because they think, "Oh, maybe I have an infection". They give a course of antibiotics by their doctor and the lymph node, maybe it goes away, maybe it doesn't. Maybe they get another course of antibiotics before somebody does a biopsy of the lymph node.

When people have more aggressive symptoms, these can be drenching night sweats, meaning you wake up in the middle of the night and your pillow is soaked, or your

nightclothes are soaked; you have to get up and change your sheets. And this is outside of the setting of infection because infection can do that. Like, let's say you have pneumonia, you can get a drenching night sweat. But, if they just continuously come and they increase in frequency, that might be an indication that something is wrong.

Same thing with fever. Sometimes people get low-grade fevers, and they often happen at night, and they happen for multiple months in a row. And, when you don't have an infection, that might be a cause to go looking for another cause for the fever.

Another clue that people might have is weight loss, and this is unintentional weight loss, and it's kind of a more significant amount of unintentional weight loss. This could be about 10% of your bodyweight over a six-month period of time. It's not just losing a few pounds here or there; it's usually a more significant weight loss.

Lastly, I would say, the really important side effect is one of fatigue. And this is a little bit of a tough side effect because, obviously, probably everyone has experienced fatigue at some point and there are lots of different causes for fatigue, but sometimes people just have this fatigue that they really can't get their day-to-day activities done, and that might be a flag that something like CLL is happening.

Elissa: Yeah. We actually recently did a podcast episode in May all about cancer-related fatigue and how it does sometimes come from the diagnosis versus how we often think it coming from the treatment.

Dr. Stephens: Yeah.

Lizette: Right. And like you're saying, a lot of these signs and symptoms are common for other diagnoses, even colds.

Dr. Stephens: Exactly.

Lizette: It's hard. It's something that people really see on an ongoing basis. So, if you have an enlarged lymph node and it doesn't go away, then it's possibly something larger.

Dr. Stephens: Correct.

Elissa: Now, what are the current treatments available for CLL?

Dr. Stephens: Well, the great part is there's lots of treatments. It's kind of an interesting cancer because you don't always need treatment right away. And so, if you come in and you actually have no symptoms or no evidence of other blood count abnormalities, like anemia or low platelets, you might not need treatment right away. That's called a watch-and-wait or an observation approach. And so, really, the very first decision you and your doctor need to make is do you even need treatment right now.

And the reason why people aren't treated right away always is because, unfortunately, we still haven't found a cure for CLL. And that's outside of the setting of really aggressive treatments, like a bone marrow transplant that someone else donates stem cells to you, which is pretty aggressive and not all people are candidates for that. But for the most part, CLL is not cured, and so I often tell people, "If I could give you something quick and easy and just cure your CLL, and then we don't ever have to talk about it again, I certainly would do that. But since I can't, the goal of doing treatment is actually to relieve symptoms of CLL."

Elissa: Okay.

Dr. Stephens: And so, if you don't have any symptoms, then that's why we don't treat because our goal is to relieve the symptoms.

Elissa: So, Dr. Stephens if a patient is on watch and wait for some amount of time and then symptoms appear that is when the disease has progressed, and patients start medication?

Dr. Stephens: Yeah, absolutely. And there are certain markers that your doctor can check to help predict how long that might be. These methods are not perfect, but there are certain molecular or biologic markers that we can check, these genetic tests in your blood to see what characteristics the CLL actually has. And then some of those are higher risk and indicate that it might be a quicker time to need treatment, and some of them might make people feel a lot better hearing about them because some of them are really low-risk characteristics, and so maybe that's a person that can actually have CLL and live out the rest of their life without ever even needing a treatment for CLL.

And, of course, we want to be careful about that because if you are in that low-risk category and you don't need treatment, we don't want to add like a bunch of side effects from treatment and that includes-

Elissa: Right.

Dr. Stephens: -financial toxicity too. All these drugs are going to cost something and so we just want to be really cautious about, if you don't need treatment, we don't want to rush into doing that.

Elissa: Right. But we've also heard from CLL patients that being on watch-and-wait or active monitoring can also be just stressful. They're constantly wondering, when is the other shoe going to drop? When is my disease going to progress to where I might need treatment? Then how will that go?

Dr. Stephens: Yeah, I know. And that's why I mentioned the term, "watch and wait". A lot of people call it "watch and worry" because I think it is really difficult to be diagnosed with a type of blood cancer and then to be told, "Hey, we're not actually going to do treatment for it right now." And so that can cause a lot of anxiety.

I've been really interested in actually looking at early treatments for CLL. There have been studies done over time with like our older chemotherapy drugs that generally

they just have a lot more side effects or toxicities. And those studies, with drugs like fludarabine or chlorambucil, some of the older drugs, they've shown that there is no benefit to treating early in terms of we don't make people live longer.

Elissa: Right.

Dr. Stephens: However, there's a big study that's going on in Europe looking at a drug called ibrutinib and seeing if that newer drug could potentially cause people to live longer by doing early treatment. And that study is still ongoing and so full results of that study are not yet published.

I'm leading a study here with the SWOG (formerly Southwest Oncology Group) Cooperative Group looking at a couple of other drugs called obinutuzumab and venetoclax. And this is a shorter therapy, so it's only one year of therapy-

Elissa: Oh!

Dr. Stephens: -and trying to find out if doing early treatment can cause people to live longer. And so, that study is called the S1925 study. It's something that can be looked up on clinicaltrials.gov and it's actively recruiting right now.

Now that study is only for people with high-risk disease and your doctor will have to go through doing the molecular test in the blood to figure out if you are high risk or not. And that's just because those people who are high risk are probably the people who would benefit the most from doing early treatment. And especially it's like, you get diagnosed with a blood cancer, your doctor tells you, "No, you're not going to do treatment", and maybe they did some tests, and they find, "Gosh, you've got high-risk disease". That's just a lot of things that can really cause people to have anxiety on a day-to-day basis.

Elissa: Now, those drugs you just mentioned those are also currently just used with normal CLL treatment, correct?

Dr. Stephens: Correct. There's a couple of different categories of treatment for CLL, what I call standard chemotherapy drugs. We don't actually use them very much anymore. Those are drugs like fludarabine, bendamustine, chlorambucil. So, what I mean by standard chemotherapy is they're drugs that we put them in through the blood or by mouth. They go in and knock out cancer cells. They also knock out good cells and that's what leads to a lot of toxicities. Some of them are really effective; they cause a lot of people to get into remission, but most people relapse, and you might cause some damage to your bone marrow, some scarring over time with these kinds of drugs. And so, we don't use those a lot anymore.

We've really shifted to these newer targeted therapies. And what I mean by targeted therapies is they're designed to go after something specific on the CLL cells. They're really more specific to CLL cells than your normal cells. And the goal of that is to kill your cancer cells and not to kill your normal cells, and hope with the goal of causing a lot less toxicity.

And these drugs have been super effective. A lot of these are actually pill medications and so, a lot of people like the idea of taking a pill instead of getting an infusion through the vein. A big class of these drugs is called Bruton tyrosine kinase inhibitors, or a BTK inhibitor. And what these drugs do is they actually are all taken by mouth. They go in and they block something that's important to the survival and growth of CLL cells. And that's called BTK or Bruton tyrosine kinase.

When I talk to my patients about it, I talk about it's almost like taking the gas out of the car. If your cancer was a car, it needs gas to go, and you're basically taking that away. But, of course, if you stop taking it away, and there's more gas, the cancer can go again. With these drugs, you actually have to take them continuously, meaning when your doctor starts you on these drugs, there's no end date. So, people say, "Does that mean I take it forever because that sounds kind of scary?" And that's not usually the case.

I usually tell people, "You're going to take it until it's not working anymore or if it causes side effects that are not tolerable." Or, the field is moving so fast, maybe we just develop a better drug, and we have a-

Elissa: Yes.

Dr. Stephens: -conversation, "Hey, there's a better drug available now. Should we switch to this? Should we try something different?"

And these specifically, the BTK inhibitors that are approved and available in the United States, are a drug called ibrutinib, acalabrutinib, and zanubrutinib, and you can tell they all end with this –inib, so that you can tell they're all part of the same class. They have a little bit different side effects between them but, overall, they're really very well tolerated. Most people have the most side effects just the first couple months they're on the drug, and then those side effects get better, and people can be on them long term. I have patients that have been on drugs like ibrutinib for almost 10 years now and doing really well with their CLL in remission and minimal side effects. So, really great drugs.

A little bit of a different approach is with a drug called venetoclax, and this is a drug, what is called, is a BCL2 inhibitor. And if you remember back when I said that when cancer happens, cells grow faster than usual and then they also don't die. And why they don't die is they express this thing called BCL2. That keeps the cancer cells from dying. It wants to help them to live forever. And so, what you do with a BCL2 blocking drug is you just allow those cells to go ahead and die. This is also a pill. It's actually very effective. Sometimes it works too effectively because if you have a lot of lymph nodes or a really high white blood cell count, you might get something called tumor lysis right after starting the drug. What that means is we kill a bunch of cancer cells really fast, and it might be a little bit difficult for your body to handle that. Your kidneys have to get rid of all those waste products like potassium and uric acid and things like that.

And so, how this drug venetoclax is given usually, maybe you'll start with another drug first so that you reduce the number of cancer cells and then you start with a really low dose. So, you start with a dose very low, 20 milligrams. You do that for a week. As long as your body is tolerating it, you bump it up to 50 milligrams. Then you do the same thing for a week at a dose of 100 milligrams, 200 milligrams and then 400 milligrams and so it takes about five weeks to get up to the max dose.

But once you're on that dose, you're stable on that dose, so just stay on the 400 milligrams. If you take it in the frontline setting, or the first treatment for CLL, we usually recommend that you do that for 12 months or one year. If you're taking it in the relapsed setting, meaning your cancer has come back after another type of treatment, we usually do 24 months or 2 years of therapy with venetoclax.

The reason why it's different and it's not given indefinitely like the BTK inhibitors because the goal of it is to kind of knock down the tumor cells really quickly. So, kill all the cells that are there, and that's what allows people to have a break from treatment after getting a deep remission.

Venetoclax is usually paired with these drugs called immunotherapies. These are drugs like rituximab or obinutuzumab, and these are intravenous, or they go in through the vein, but they're immunotherapies. They're not like the classic chemotherapies that I talked about. They look for something called CD20 which lives on the surface of CLL cells, and they either kill those cells directly or they tell your immune system to kill those cells. That helps you to get a deeper remission along with venetoclax. And so usually when you do it in the frontline setting, you might use it with venetoclax with obinutuzumab. If you're doing it in the relapsed setting, right now it's just approved to use rituximab in that setting.

All of these drugs are really fantastic options that have way less side effects than the old kind of standard chemotherapy drugs and they're causing people to go into remission for really long periods of time. They're really a win for any patient with CLL.

Elissa: That's great.

Lizette: Yeah, I think it is great that there's so many different options now for patients. A lot of times CLL patients will ask us, "Is there a certain order that we have to take these medications, or how does my doctor choose which medication I take at which point in time?"

Dr. Stephens: These are all great questions, and we don't actually have the complete answers to all of them at this time. And so typically what has happened over the last few years is people get started with the BTK inhibitors, just because those were approved well before venetoclax was approved, and so a lot of times you see somebody takes a BTK inhibitor, like ibrutinib, and then maybe they have relapsed disease, and then they go onto receive a venetoclax-based therapy.

But, recently we've started using venetoclax and obinutuzumab earlier in treatment. People tend to like the idea of having a shorter treatment, so only a year as opposed to indefinite treatment. There have been some studies that say it does look like venetoclax works really well after using BTK inhibitors; and it also looks like BTK inhibitors work really well after using venetoclax.

And so there might not be a right answer. What I do when I tell a patient that they need treatment, we go through the options, and we look at other medical problems. Maybe there's some other medical issues that would steer me in the direction of venetoclax versus a BTK inhibitor or vice versa.

And so, just looking overall at cost of the medications, the length of therapy, the other medical problems that a patient might have. I spend a lot of time talking with patients because we have so many options just fleshing out, you know, these all work well; but here are the potential side effects of this. Here are the potential side effects of this. The goal of this is to take away your symptoms and help you live your life. So, what side effects seem like they would be tolerable for you?

There's a lot of discussion and shared decision-making between the doctor and the patients. Because we have so many good options, there's not a clear answer. And there's a ton of clinical trials that are ongoing right now that say these two classes of drugs, BTK inhibitors and venetoclax, the BCL-2 inhibitors, they're great classes of drugs. Should we be using them together, upfront, to get deeper remissions, or does it still make sense to use one than the other? A lot of those trials are still ongoing, so there's a lot of answers that hopefully will be coming over the next couple of years about what's the optimal way to sequence, how many do we need? If one drug is good, is two drugs better? Are three drugs better? Should we be using obinutuzumab along with these drugs in the frontline setting? A lot of unanswered questions, but all in all still very great results from all of these treatments.

Lizette: Sure. And I'm glad that you're weaving into the discussion for treatment quality of life because, as you say, the goal of the treatment is to provide a better quality of life for patients.

Dr. Stephens: Exactly.

Lizette: Now for CLL, is stem cell transplantation or even CAR T-cell therapy options for treatment?

Dr. Stephens: They are options, and I should say with the caveat that CAR T-cell therapy is not approved by the FDA (Food and Drug Administration) in the United States for the indication of chronic lymphocytic leukemia, but there are lots of clinical trials that are ongoing there. So, that would only be an option right now on a clinical trial. Whereas if a bone marrow transplant or stem cell transplant is indicated, that is approved; and that is something that can be done through a patient's insurance right now.

There's a rare patient that still needs a bone marrow transplant. We used to do it a lot more frequently when we didn't have all of these new drugs that work really well. And

the reason why we're very cautious about recommending a bone marrow transplant is that tends to have a lot of side effects or toxicities.

What a patient needs to do for that is they need to undergo some really intensive standard chemotherapy drugs that completely knock out their immune system and then have somebody else's stem cells donated and infused through the blood. Those stem cells from another person, they'll go in and they'll set up shop in the bone marrow and, hopefully, kind of replace the immune system; and they have an effect called graft, which means the stem cells that are transplanted versus leukemia. They're in there constantly saying, "Hey, this is not normal. We need to fight you and get rid of you."

That process, when their immune system is low, it lasts for about a month. Infection is critically important during that time because if the patient gets an infection, they could even die from an infection because their immune system is so low.

Some patients also experience something called graft-versus-host (GVHD) when the stem cells from somebody else start to think that the patient is something foreign and attack them. And you can get things like skin rashes, diarrhea, irritation in the eyes, the lungs, the liver. If that happens, it can cause people a lot of side effects.

It is a really good treatment, and it can lead to cure in some people. But it just has a lot of side effects, and we generally don't offer transplants to people over the age of 65 or 70. And whereas the average age at diagnosis of CLL is somewhere between 70 and 72. And so, a lot of patients just right off the bat are not even candidates for this because it's so toxic. I always tell people my goal is to kill the cancer and not to kill you. And sometimes the side effects of that can be really strong.

The other tough part is your CLL has to be in a very good remission to do a transplant. So, you already have to have shown that your disease is responsive to treatments; and sometimes people who, maybe they've gone through five or six different lines of treatment, it's really hard to get their CLL back into remission. If you can't get into a

remission, the chances of a stem cell transplant working are very low. And so, if we can't get into a remission, then we don't do the transplant.

There's another type of transplant called autologous stem cell transplant; and that's when you donate your own stem cells. Basically, we pull your cells out, put them in a refrigerator, for lack of better medical terms for it, and then give chemo and put them back in. I generally only recommend that for somebody who has Richter's transformation, which is when their CLL turns into more aggressive lymphoma. And the goal of that is more to cure the Richter's, that lymphoma part, than it is to cure the CLL. The reason why we might do that is because people, older can get that kind of transplant. It's not quite as toxic.

And in terms of CAR T, like I said, it's still only available on clinical trial. As you know, that's when we take a patient's own blood cells and separate out the T cells part of the immune system and essentially train that in the lab to go after something that lives on the surface of CLL cells. Most commonly CD-19 is what we would be using right now.

This does work. It can often put people into remission. But there are side effects associated with it, and so again, not everybody might be a candidate for it. You can get something called cytokine release, which means we really overactivated your immune system, and you can have problems related to that. You can get neurotoxicity, and sometimes that's like confusion or even loss of consciousness, things like that.

We know a lot better how to deal with these side effects so we can get people through them. But the problem we're finding in folks with CLL is that they do work. They put people in remission you can be in remission for two or three years and then, unfortunately, the CLL can still come back after that.

We got very excited thinking, "Oh my gosh, these patients that had no other options, we can put them in remission. Maybe this is a cure for CLL." And it doesn't look like it. There are certain patients that do have very long responses at this timepoint, but

we don't know how to pick what patient is the one that's going to get the long response. And so, there's still a lot of clinical trials going on trying to figure out how do we make CAR T cells better for people with CLL?

Elissa: So, you mentioned just now and earlier about side effects with these different medications, and also Lizette mentioned the quality of life. So, since CLL is a chronic disease, life-long, what can you do for side effect management and to help that patient have a good quality of life?

Dr. Stephens: Great question, and it's usually quite individualized from one person to another; and it depends on what side effects you're having. With the Bruton tyrosine kinase inhibitors, I had mentioned that some of the side effects come early. And those side effects are usually things like nausea, diarrhea, and even sometimes skin rashes. Those things are usually pretty easily managed, so you can take antidiarrheal agents, you can take antinausea agents, and those side effects usually go away. With a skin rash, maybe you need a little bit of hydrocortisone cream or in more severe cases, maybe you need to take some oral steroids. But those will go away.

Things that don't go away. There is bruising and bleeding that come with these BTK inhibitors, and those are things that usually, if it's not severe, it's just something a patient has to live with. And usually people are able to work around that side effect.

If it's more severe bleeding, like occasionally people have bleeding, like bleeding into their joints or into the skin tissues or maybe they need to have a surgery, so we just counsel people to hold the drugs around the time of surgery to prevent any bleeding problems. In those more severe cases of bleeding, I often will reduce the dose of the drug or potentially change to a completely different class of drugs to reduce that risk of bleeding.

The other thing that can happen with the BTK inhibitors is you can get a heart arrhythmia called atrial fibrillation, which is when your heart beats kind of fast and it's racing. And that often requires co-management with a cardiologist or a heart doctor.

Usually, we have to give you medications to keep the heart rate down. Maybe you would get a shock to your heart to get your heart back into rhythm, things like that, but usually it can be managed.

The other thing that happens over time on these drugs is you can get high blood pressure, and so often we might just need to add in drugs to lower the blood pressure. The good thing about these drugs too is that they are very short-acting; and that's why you have to take them every day. So, if somebody's having a side effect and we can't tell, is it due to the drug or is it something else, I might just have them hold the drug for a week. So don't take the drug for a week. By then the drug should be mostly out of your system. And if it is the drug causing the side effect, that side effect should get better.

And then, by holding the drug, if that makes the side effects go away, oftentimes I'll start back with a lower dose of the drug and see if people can tolerate that lower dose.

One side effect that I should mention that's unique to acalabrutinib is a headache, and about half the people who are starting that drug will get a headache; and this is one that is worse during the first month or two on treatment and will get better with time. People can treat that with medications like Tylenol®, and they can drink additional caffeine; and that usually is enough to get those side effects to go away.

Conversely, with venetoclax, they have a different set of side effects. I mentioned the tumor lysis, which is why we ramp up the dose slowly. The other thing that can happen is low white blood cell count, which can make you at higher risk of infection. Sometimes, I have to give people shots, like growth factor injections to help boost the good white blood cell count back up.

The other thing that can happen with venetoclax is sometimes people get nausea or diarrhea. I often find that those side effects are better if you take your venetoclax dose at night, so maybe it's just that you're like sleeping through the nausea.

The other thing, if you take it at night and then you take an antinausea medication, which generally causes a little bit of sedation, people might just sleep through the part that causes the nausea; and people are able to tolerate it pretty well.

It is really important, especially with the BTK inhibitors, because, as a doctor, I'm asking my patients to take these for a really long time. You have to tell your doctor what side effects you're having because if you don't tell them, your doctor can't help you with them. Your doctor's job is to help you with side effects. And I always tell people, I'm the reason why you're having these side effects because I'm giving you this drug. So, I would be happy to help you get rid of this side effect. People just have a lot of options, and so shouldn't be sitting at home suffering from side effects; and we have other things that we could do that could provide a better quality of life.

Lizette: Sure. Is there any new and emerging treatments that you're particularly excited about right now for CLL?

Dr. Stephens: Yeah, I think the exciting part is, there's so many drugs that are new and coming forward in various stages of clinical trials.

I'll take a couple minutes to talk about the most advanced one, which is a drug called pirtobrutinib, and you might recognize that sounds a lot like ibrutinib, acalabrutinib, and zanubrutinib.

Dr. Stephens: So, it's the same kind of drug. It's a BTK inhibitor, and it actually got approved at the very beginning of 2023 for a different type of blood cancer called mantle cell lymphoma. So, it's out and available on the market, but just not for CLL.

Sometimes your doctor could get this off label or there's still a lot of clinical trials that are ongoing with this drug. Basically, it's a pill. Again, you take it daily; and meant to be indefinite. A couple great parts about this drug, when people's CLL develop resistance to the other types of BTK inhibitors, it's usually a specific mutation that causes people not to respond to any of those three currently approved drugs. This

drug, pirtobrutinib, can work around that. It binds at a different site. And so even if you had resistance to say acalabrutinib, you would still have a good chance of responding to pirtobrutinib.

And so, the other great part about this drug is it doesn't have a lot of side effects. People tolerate this drug really well, and so I think that's a really added benefit and helps people with their quality of life.

There are clinical trials right now. A lot of data in people with relapsed disease, but there's clinical trials also looking at moving it to earlier stages of treatment for CLL.

A lot of other drugs ongoing. There's these drugs called degrader drugs, and so basically what they're trying to do is they're trying to degrade or take away, so eat up whatever protein the drug is targeting. And they also have these degrader drugs that target BTK, and they're kind of interesting because most of this resistance develops through binding site mutations. Well, if you just degrade the whole protein, you don't have to worry about what site it binds to. You're just taking away the whole protein in general. And so those are in a little bit earlier stages of clinical trials, but really exciting drugs. Just a lot of great research going on in the field for patients with CLL.

Elissa: That's great. Well thank you so much, Dr. Stephens, for joining us today. I really loved this discussion about CLL. I think there are so many amazing options for CLL, and it sounds like some great ones around the corner.

I love hearing about the degrader drugs. I haven't heard of those before, so that was fascinating. So, thank you so much for being here with us today. We really appreciate it.

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

Elissa: And thank you to everyone listening today. *The Bloodline with LLS* is one part of the mission of The Leukemia & Lymphoma Society to improve the quality of lives of patients and their families.

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In addition to the lounge, we could use your feedback to help us continue to provide the engaging content for all people affected by cancer. We would like to ask you to complete a brief survey that can be found in the show notes or at TheBloodline.org. This is your opportunity to provide feedback and suggested topics that will help so many people.

We would also like to know about you and how we can serve you better. The survey is completely anonymous, and no identifying information will be taken. However, if you would like to contact LLS staff, please email TheBloodline@LLS.org.

We hope this podcast helped you today. Stay tuned for more information on the resources that LLS has for you or your loved ones who have been affected by cancer.

Have you or a loved one been affected by a blood cancer? LLS has many resources available to you – financial support, peer-to-peer connection, nutritional support, and more. We encourage patients and caregivers to contact our Information Specialists at 1-800-955-4572 or go to LLS.org/PatientSupport.

You can find more information on chronic lymphocytic leukemia at LLS.org/Leukemia. All of these links will be found in the show notes or at TheBloodline.org.

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