LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Emerging Therapies and Hope: Diffuse Large B-cell Lymphoma'

Description:

Diffuse large B-cell lymphoma is the most common subtype of non-Hodgkin lymphoma. Tune in as we chat with Dr. Yasmin Karimi from the University of Michigan about the latest breakthroughs in treatment, including combination therapies, CAR T-cell therapy and bispecific antibodies. Discover how these innovations are offering new hope and pathways to cures for patients.

Transcript:

Elissa: Welcome to *The Bloodline with LLS*. I'm Elissa. Thank you so much for joining us on this episode. Today, we'll be speaking with Dr. Yasmin Karimi, a Clinical Assistant Professor of Medicine in the Division of Hematology/Oncology at the University of Michigan. She is a Clinical Investigator with a research focus on B-cell lymphomas such as diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, and Hodgkin lymphoma. Welcome, Dr. Karimi.

Yasmin Karimi, MD: Thank you so much for having me here today.

Elissa: So, our episode today is on diffuse large B-cell lymphoma, a type of non-Hodgkin lymphoma. Could you tell our listeners what that is and how that is different from Hodgkin lymphoma?

Dr. Karimi: Yeah, that's a great question. So, usually the way I describe it is, lymphomas in general is an abnormal growth of a type of normal white blood cell called the lymphocyte. So, we know how normal lymphocytes help as part of our immune system. They help us fight off infections and when they become abnormal, become cancerous, that's how they become lymphomas.

In general, there's two main types of lymphoma. There's something called Hodgkin lymphoma, and then everything else gets lumped under non-Hodgkin lymphoma. So, Hodgkin lymphoma is actually one of the first ones that was diagnosed. It was actually mistakenly diagnosed as tuberculosis back in the day, and that's just based on the abnormal cell types that were seen under the microscope. And that's why everything else gets bunched under non-Hodgkin's, because it's the one that didn't look like the Hodgkin lymphoma.

Elissa: Okay.

Dr. Karimi: That's the first split that we have; and then the non-Hodgkin lymphoma, there's many different subtypes. Generally, we say, okay, there's the B-cell lymphomas and the T-cell lymphomas and how we tell those apart is really based on some of the markers that we see under the microscope and using some of our blood testing that we do. And then within non-Hodgkin's B-cell lymphomas, we start talking about the aggressive lymphomas and then the more slow-growing lymphomas. And like I said, there's over 70 different subtypes of all these lymphomas.

Elissa: Okay. So, speaking of the aggressive and slow-growing, or indolent, lymphomas, how is diffuse large B-cell lymphoma categorized and what does that mean in terms of the type of treatment and prognosis?

Dr. Karimi: So, diffuse large B-cell lymphoma is the most common type of non-Hodgkin lymphoma. It accounts for over 40% of the cases that we see. So, it's actually one of the most common lymphomas that I see in my practice.

How do we know it's aggressive? How do we know it's diffuse large B-cell lymphoma? That has to do with the biopsies that all our patients get before they're able to get a diagnosis. So, under the microscope, we look at the cells. It usually has to do with, we see large cells, hence, the name diffuse large B-cell lymphoma. And then, we look for specific markers that just convince us that, yes, this is this specific type of lymphoma.

How is it different than indolent lymphomas? Well, it's different in many ways. Starting from under the microscope, it just looks different. So, these are large cells versus the slow-growing indolent lymphomas generally have smaller or medium-size cells. And then there's other characteristics about how it looks under the microscope that make us differentiate the diagnosis. And then what we're seeing, in terms of what we see in the clinic, these patients who have indolent lymphomas or slow-growing lymphomas tend to have it come up incidentally found on scans or they just happen to notice it one day. And it's not rapidly enlarging, it's slowly growing over time versus the diffuse large B-cell lymphoma tends to be people who feel like the lymph nodes or the masses are growing rapidly over time, and it tends to be people who just are sicker or end up becoming sicker if the disease is not treated quickly.

Elissa: So, let's discuss the current treatments for diffuse large B-cell lymphoma. Now, before we really get into all the treatments, you talked about the difference with the slow growing versus aggressive. For slow growing, is it more quality of life and aggressive more really trying to get into remission and potentially curative?

Dr. Karimi: Exactly. You're exactly right. So, what we know with the slow-growing lymphomas is, it was so slow growing, people said, way back when, "Well, what happens if we don't treat this right away? What happens if we watch it?" And so, we did clinical trials where we took all patients who were diagnosed with slow-growing or indolent lymphomas, and we took half of them and we treated them the first day they were diagnosed. We took the other half of them, and we waited and we only treated those patients if they had symptoms or reasons, like medical reasons for treatment. And Elissa, let me ask you. What do you think happened if we watch those patients for 10, 20 years? Any guesses on how those two groups of patients did, the ones who we watched the long term and the ones who we treated right away?

Elissa: I would assume the ones you treated right away probably had a lot of side effects, and then the ones that were just watched long term probably had a good quality of life, were able to live normal lives.

Dr. Karimi: Yeah, you're exactly right. We know treatment, you can have more side effects. And ultimately, what we saw that was kind of the reason why we do what we do now for low-grade lymphomas is that both groups lived the same amount of time. So, whether you got treatment right away in the first year you were diagnosed with the slow-growing lymphoma, or if we waited until let's say, you were having symptoms or low blood counts or reasons for treatment. Other things we think about is like when it's impacting other organs. So, if you have lymph nodes that are pushing on the kidneys or impacting your ability to breath or causing you to cough, all those are very much reasons that we would start treatment. But if you don't have one of those reasons, that we know it's very safe to monitor people who have slow-growing lymphomas and that those patients that we monitor will live just as long as patients that we treat right away at diagnosis in terms of when they need treatment down the line.

Elissa: Yeah. Whereas an aggressive lymphoma, like diffuse large B-cell lymphoma, we want to start treatment right away to get this under control, correct?

Dr. Karimi: Exactly. So, with aggressive lymphomas, unfortunately, if we monitor these aggressive lymphomas, we know that patients would get very sick very quickly. And so, the goal is as soon as we find that there is an aggressive lymphoma, we do not wait. We do not watch. Sometimes patients are having minimal symptoms, even then we say, "We know this is aggressive. We know that this is something that would progress over time," and so, we will try to treat them as soon as possible after we find the diagnosis and, obviously, getting all the right workups started before we start treatment.

Elissa: Are these treatments potentially curative?

Dr. Karimi: They are. We are fortunate enough that we have really good active therapies; and we can cure anywhere between, we generally say our average is 70% of patients who are diagnosed with an aggressive lymphoma. That number ranges

anywhere between 60 to 80+%and that really depends on some of the risk factors that we can identify in patients to know how successful we think their treatment is going to be. And so, we hope that with treatment, it is a combination of chemotherapy and immunotherapies, but with that combination of therapy that we can cure, on average, about 70% of patients with diffuse large B-cell lymphoma.

Elissa: That's wonderful. Now, what are those risk factors that you talked about?

Dr. Karimi: Yes, so there's a scoring system called the IPI (International Prognostic Index) score, and it's actually something that's been developed many, many years ago but involves the combination of knowing the patient's age, what stage they are, how many sites of disease they have on their scans, and in terms of how many sites outside of the lymph nodes are involved. We also use some laboratory markers, something called the LDH or lactate dehydrogenase. It's one of the common labs that we test in patients with lymphoma. And then, also looking at how fit and healthy the patient is at the get-go from all this. But combine all these things, and it gives us a score; and that IPI score tends to correlate, on average, not for every patient, but gives us a sense of how successful we think that patient's treatment is going to be.

Elissa: Okay, so are you using then that score to choose a treatment or is it a standard treatment that everybody gets?

Dr. Karimi: That's a really good question. Up until a couple years ago, we actually weren't choosing treatments based on the scoring system. So, all patients, regardless of score, got the same treatment. In the last couple of years, the clinical trials that have been done have actually used this IPI score to say, "Okay, if you have a low-risk IPI score, we know you're going to have a really good, 80-90% chance of long-term cure so, let's give you our standard treatments." Like I mentioned, it's that combination of drugs, R-CHOP is the common regimen that we use.

In patients who have a higher-risk score, we say, "Well, if your IPI score is 2, 3, 4, or even 5, we know that while we still can cure you, we worry that cure rate is going to

be a little bit lower. So, can we include additional treatments with the R-CHOP therapy to improve the overall success and cure rate of treatment? And so trials recently, the POLARIX trial using polatuzumab vedotin – I know it's a long word, but it's an antibody that's linked to a drug that we give with the R-CHOP therapy. We substitute one of the drugs for the polatuzumab. And the newer studies that are ongoing right now are even looking at combining other types of immunotherapies, so things like bispecific antibodies or using additional types of immune therapies like CAR T-cell therapies earlier in patients who are really high risk for progressing with the R-CHOP therapy.

Elissa: Okay. So, before we get into bispecifics and CAR T-cell therapy and talk about what those are, so a first-line treatment, generally, whether it is, low score or higher-risk score, would be either just R-CHOP or R-CHOP and a combination with something else?

Dr. Karimi: Yeah, so right now the standard of care for low-risk patients would be R-CHOP. For higher-risk patients, we think about adding the polatuzumab vedotin; and there's some nuances based on the types of cells that we're seeing and with something called cell of origin or what subtype of the diffuse large B-cell lymphoma it is. It sometimes informs whether or not we decide to use the polatuzumab vedotin or not.

And then the other thing we think about is, is there a clinical trial that's available for patients? Clinical trials are how we develop new standards of care in therapy and so, if there is a clinical trial available, we generally will try and offer it to patients, especially high-risk patients because we worry that those are the patients that are going to be the highest risk for this coming back, even with the intent to cure them with the first line of treatment.

Elissa: Now, I want to make sure, so patients know, when you're talking about clinical trials, this doesn't mean that you've run out of options, right? This is something that could just introduce you to a new potential drug that could help.

Dr. Karimi: That's exactly right. So, clinical trials are being conducted at all stages. We generally, you're right, most often think about clinical trials when you run out of options. So, those are trials that are being done in patients who have relapsed on multiple lines of therapy and we're trying new drugs that maybe haven't been tested before.

The types of trials we test in patients who are newly diagnosed and are getting first treatment, are generally treatments that have already been studied and proven to be effective in that disease and proven to be safe, in patients with that disease. And the questions we're asking is, well, if we move that treatment that we know is so effective, but we use it right now in third or fourth treatment, what if we move it to the first treatment? Can we make our first-line treatments even more effective by bringing those very active, effective drugs earlier into the treatment space?

Elissa: Okay. Now, let's talk about the bispecifics and CAR T-cell therapy. So, these are immunotherapies. Could you tell our listeners what both of those are?

Dr. Karimi: Yeah, and this is the most exciting part about lymphoma right now, is all the ways that we are developing to try and target and kill these lymphoma cells. We know that the immune system plays a very large role in helping us to be able to clear cancer cells. And this is true, not just in lymphoma but in many of the types of therapies. So, this actually all started in melanoma when they realized that these immunotherapies were very effective.

So, in non-Hodgkin lymphoma, there is a type of therapy where you can take your own immune system cells, your own T cells and engineer them to fight off your cancer. This is called CAR T-cell therapy. So, you take your own body's T cells. They pull it out using an IV. They engineer them to try and find and destroy your own body's lymphoma cells by targeting a molecule called CD19 that is present on almost all our lymphoma cells. So, that is what the CAR T-cell therapy is.

CAR T-cell therapy has been tested now for many, many years and was approved first in I think, 2017 for the treatment of diffuse large B-cell lymphoma because of how active it is. And then over the years, we've actually been studying it earlier and earlier in the treatment course, taking effective therapies and seeing if we use them earlier can we cure patients earlier in the disease course. And so, CAR T-cell therapy, right now, is approved and would be the standard-of-care treatment for patients who relapse after the first treatment, if they relapse within the first year or so after their R-CHOP therapy.

Elissa: And so, it is not a first-line treatment?

Dr. Karimi: So, right now it is not approved for first-line treatment, but it is one of the things that we are looking at in clinical trials is if we take patients, particularly the patients who are very high risk, so we're talking about IPI 4 or 5 patients, and we treat them with CAR T-cell therapy as part of their first-line treatment, can we cure more patients than we would with just the R-CHOP alone? So, right now it's approved in the second line setting and in the third-line setting for patients who relapse with a diffuse large B-cell lymphoma, but hopefully ongoing studies will tell us how it may or may not impact treatment earlier.

Elissa: And then, what about bispecifics? What is that?

Dr. Karimi: Yes, so bispecific antibodies is kind of what the name implies. So, bi means it has two arms to it. One arm targets your own body's T-cells, so something called CD3, a marker on your own body's immune system cells. The other part of the bi is the marker that is on your tumor cells, something called CD20. And what it does is think about a molecule that has two arms. One arm grabs your own system's immune cells, the CD3 cells. The other grabs your lymphoma cells, the CD20 cells, and says, "Hey, immune system, take a look here. We have a lymphoma cancer cell that shouldn't be here. Kill it." And essentially it does that. It induces an immune system reaction to kill your lymphoma cells using your own innate immune system.

And so, that is what bispecific antibodies are. The ones that are currently approved are targeting the CD3 and the CD20, but there are ongoing studies looking at different combinations and different targets for these bispecific antibodies.

Elissa: Wow, that is really exciting. So, with all of these different treatments, the R-CHOP and the immunotherapies, what side effects may patients have from treatment, and are these side effects manageable?

Dr. Karimi: Yeah, obviously, the goal here is to cure these patients with this treatment. So, if the goal is to cure them, we don't want to do it at the expense of having long-term side effects.

So, the biggest thing we think about short term is, unfortunately, because of the types of treatment that we're using, the chemotherapy treatments, patients do lose their hair. That's something that is a source of distress for a lot of patients. Patients will lose their hair.

The most common thing we see is low blood counts, which can increase the risk for infection. So, infections complications are something that we commonly see and counsel patients about when they're on chemotherapy.

Other side effects that we can see, we can see numbness and tingling in the hands and feet. We can see a little bit of nausea, diarrhea, constipation. All these side effects, in general, tend to be pretty manageable. If patients are having side effects, a lot of good medications that we can use to intervene and to help improve those side effects and turn things around for patients.

The other common thing that we see that we, unfortunately, don't have a great solution for, is fatigue, so fatigue is something that people do experience. It tends to be worse in the middle of the cycle of treatment, right when the blood cell counts are their lowest, and then tends to improve right before the next treatment.

All things considered, this is a relatively well-tolerated treatment option. We have patients who are young and continue to work while they're on treatment. Patients who are older, sometimes they still are also working on treatment. I do find that older patients tend to just need a little bit more naps or tend to sometimes feel the side effects a little bit more. But, in general, all these treatments are well-tolerated.

They're all given in the outpatient clinic. So, the patients do not need to be in the hospital for these treatments. They can be treated in the outpatient setting. It's one day every 21 days for the R-CHOP therapy. And so, in general, people can still maintain their quality of life. They can be with their families. They can enjoy holidays with their friends and family, just while all being careful about particularly the risk of infection during this time.

Elissa: Yeah, absolutely. And speaking of the holidays coming up with low blood counts and the potential of COVID rising, what should patients be thinking about with that?

Dr. Karimi: That's a great question, and it comes really commonly. Some patients are really nervous about being out in public with the compromised immune system. Anyone who's on chemotherapy has a compromised immune system. And I think it's a little bit heightened in our patients with lymphomas because the rituximab drug, the R drug that we use with the R-CHOP is one of the ones that actually can deplete the immune system's ability to fight off viruses. And it's not just something that happens during therapy. It certainly happens during therapy, but it can happen even for months after you finish therapy, just because of how effective the treatment is on killing those good lymphoid cells, the ones we need as part of our healthy immune system.

So, what I generally tell patients is, I say, "You're on treatment right now, and you have to be careful." But, I never want patients to put their lives on hold or to stop doing things that they would normally find enjoyment and joy out of, right? We're

doing all of this because we want to improve their quality of life and give them their lifespan and their quantity of life back too.

So, just being careful. Washing your hands. If they're in a public place, wearing a mask as much as possible. If they're in a place where they can control who's around them, just making sure the people who are around them are not coughing and sick and having fevers. We do recommend to all our patients that they get their flu shot, COVID shot, RSV shot, get up to date in all their vaccinations, do everything they can to protect themselves, as well as to have the people around them, so their friends and family also get vaccinated to almost create that herd immunity around the patient who's immune compromised.

I had patient yesterday ask me, "Is it okay if I go to church?," and I say, "Yes, you just have to be careful. You have to be careful about the people around you and just be mindful of these things." But grocery shopping, going to places of religious worship, being around friends and family for the holidays, being around grandchildren or children who may be coming home from school or daycare with, with sicknesses and illnesses, I say, "You just have to be mindful and be careful. Wash your hands. Ask everyone around you to wash their hands. But don't let it take you away from the people and things that you love."

Elissa: That is very good advice. So, you mentioned the side effects for R-CHOP. Could you talk about side effects for bispecifics and CAR T-cell therapy?

Dr. Karimi: Yeah, the side effects that we see with this type of class of immunotherapies is a little bit different than what we see with traditional chemotherapy. The biggest thing we see is we see activation of the immune system. I'll talk about CAR T first because that's the one that's the easiest and best well-defined at this point with the longest-term data.

The most common thing we see is something called cytokine release syndrome, or CRS. And it's basically an overactive immune system, right. You're using the immune

system to rev up and fight off the cancer cells and in the process, if it gets too revved up, it can create this overdrive of the immune system. That can manifest in symptoms like fevers, a little bit of low blood pressure, difficulty breathing. And if the inflammation happens in and around the brain, it can also create confusion or symptoms of something we call neurotoxicity. So, those are things that we are very vigilant for, we keep an eye out for. And the rates of those toxicity, how often they happen, and how severe they are really just depend on the type of CAR T-cell you're getting and the type of bispecific antibody you're getting.

In general, we see the same types of side effects with CAR T, the cytokine release syndrome and the neurotoxicity with the bispecifics as well. But the bispecifics actually have a much lower incidence and severity of some of those toxicities, and it just has to do with the fact that we're able to use a lot of pre-medications and strategies to kind of lower that risk with the bispecifics that it's just harder to do with the CAR T-cell therapy.

You still have the same risk for the immune system being lowered and being immunosuppressed, low blood counts. That same risk still applies to both the CAR T-cell therapy and the bispecific antibodies. It's something that we remain vigilant about whenever patients are on any of these treatments.

Elissa: That is very good to know. So, let's move onto the future of treatment. You discussed a little bit of clinical trials, but are there any emerging therapies or currently in clinical trials that you're particularly excited about?

Dr. Karimi: That's a great question, Elissa. So, we've had nine treatments that have been approved for relapsed/refractory diffuse large B-cell lymphoma in the last seven years. The things I'm most excited about is, like we talked about the bispecific antibodies, so epcoritamab and glofitamab have both been approved for the treatment of relapsed/refractory disease and shown really promising response rates in patients who have had multiple prior lines of treatment, including CAR T-cell therapy.

We're also seeing combinations of treatments, so combinations of bispecific antibodies, plus other things that have been used earlier in patients who may not be even fit for or eligible for CAR T-cell therapies. We're seeing safer use of the CAR T-cell therapy. So ways we can make the CAR T-cell therapy safer and more accessible to more patients. We're seeing different versions of CAR T-cell therapies targeting different markers. So, something called the CD22 CAR T-cell therapy, something that now is ongoing in research and we're learning more about the efficacy and safety of this.

We're also looking at more ways we can modulate the immune system. So, there's a class of drugs called CELMoDs (cereblon E3 ligase modulatory drugs) that are being looked at in diffuse large B-cell lymphoma to see if this alone or in combination with other drugs can be used to safely and effectively treat the diffuse large B-cell lymphoma.

And I think that overall, I we're learning about better ways to monitor diffuse large B-cell lymphomas. So, we traditionally were using PET scans. Now, we're getting more and more information about using something called circulating tumor DNA, where we basically take a blood test and we can see very, very small amounts of diffuse large B-cell lymphoma cells that are still left in the blood. And this can help us maybe identify patients who are at risk for the lymphoma coming back. Maybe even develop ways that we can treat them sooner and provide ways that we can monitor their disease after treatments.

Elissa: Wow. That is all just so exciting. I'm really interested to hear about all the different treatments that are available and the changes that are coming up with CAR T-cell therapy and that really good potential with bispecifics.

So, our final question today, on our patient podcast home page, we have a quote that says, "After diagnosis comes hope." What would you say to patients and their families to give them hope after a diagnosis of diffuse large B-cell lymphoma?

Dr. Karimi: That's a really nice quote. I think that I would say, that no one ever wants to be in a place where they're dealing with a cancer diagnosis for themselves or for their friends or family. We are at a fortunate time in lymphoma where we are curing patients with this diagnosis. We're at a time where we're developing more active, safe, effective treatments to hopefully improve the cure rates, make these treatments more tolerable, and allow patients to live their lives while on treatment and go back to as much of a normal life as possible after treatment.

So, I would tell them to keep having hope, to stay engaged in their treatments, to stay active and do everything thing they can. That's what sometimes people ask us is what can I do? "We're in this phase of my treatment plan. What can I do to make my outcomes better?" And the biggest thing we tell people is just stay healthy and active physically and mentally. Do everything you can to put yourself in the best position to allow your body to fight off the cancer.

I wish we had better ways of predicting who's going to respond to treatment and who doesn't, and we're not there yet. We can't tell people at the get-go whether or not we think that this treatment's going to work or not. And there's nothing, unfortunately, that people can do. People ask us about supplements. People ask us about whether or not they can still eat sugar, whether or not they can, you know, go out and go swimming or things like that. And I say, "Unfortunately, there's no good data on any herbal remedies or any type of supplements. There's no data that we know of that sugar feeds cancer." So, I tell people to enjoy their chocolate cake and their French fries and enjoy the things that they love, but just to keep a hopeful attitude, keep a positive mindset, and keep their bodies and their minds healthy during their treatment process.

Elissa: Yes. And after all the things that you said about the treatments and upcoming treatments, I think there is a lot of reason for hope and nine new treatments in just a few years is so exciting.

Well, thank you so much, Dr. Karimi, for joining us today and telling us all about diffuse large B-cell lymphoma. I hope that you gave these patients a lot to think about and be able to go back to their doctors with this information. So, thank you so very much.

Dr. Karimi: Thank you for having me here.

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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