

## THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

### ***Episode: 'CLL: Transformation in Treatment'***

#### **Description:**

Join us as Ellin Berman, MD a leukemia expert from Memorial Sloan Kettering Cancer Center discusses the advancements in treatment for Chronic Lymphocytic Leukemia (CLL). Dr. Berman explains how not all CLL is the same, as it is a heterogeneous disease which explains why one person's CLL can act differently from another person's CLL. Dr. Berman speaks about how some patients do not start treatment right away and why some patients may be good candidates for clinical trials. Every patient is different, and since there are newer treatments now available for CLL, Dr. Berman provides patients with different treatment options, and encourages patients to ask questions and to be a partner with their treatment team when making treatment decisions.

#### **Transcript:**

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

**Edith:** I'm Edith.

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

**Alicia:** Today we will be speaking with Dr. Ellin Berman. Dr. Berman is a Board-Certified medical oncologist and hematologist with a clinical and research focus on new drug development in acute and chronic leukemias. Welcome, Dr. Berman.

**Ellin Berman, MD:** Welcome everyone.

**Alicia:** So, before we jump in, we always love to get to know our guest speakers a little bit more. Our listeners also appreciate that as well. We just want to know what brought you to the field of medicine, specifically hematology and oncology?

**Dr. Berman:** So, when I was an intern and a resident at Boston University Medical Center, I gravitated to the oncology floor and had the opportunity to work with really some wonderful groundbreaking hematologists there; sparked my interest. And I just knew that I wanted a career in hematology. I was fortunate enough to be accepted in the fellowship program at Sloan Kettering. Really found it a wonderful place to work, and 40 years later still think the same. So, I really credit my early teachers, my early instructors both in medical school and in my residency for opening the door. Never regretted it.

**Alicia:** That's awesome! Forty years. Congratulations!

**Dr. Berman:** Thank you. Well earned.

**Alicia:** Exactly, exactly. On today's episode, we'll be speaking about chronic lymphocytic leukemia, also known as CLL. What is leukemia and how does it develop into CLL?

**Dr. Berman:** So, leukemia is actually a broad term for a number of different types of blood cancers. And when I talk to patients with newly diagnosed leukemia, what I usually say is that it's a type of cancer of the blood cells that are made in the bone marrow; and there are many different types of leukemias. We generally divide them into the chronic leukemias and the acute leukemias. And there are a number of nuances within each of these diseases, so it's really a very large field; and there are many types of doctors, oncologists, and hematologists to care for people with leukemia. What I would suggest though, if you do have the diagnosis of leukemia, is to seek out a physician who cares for people with this specific illness.

**Alicia:** Interesting. And so how does it develop into CLL?

**Dr. Berman:** So that's a very big research question. We actually don't know how people develop leukemia. There are some established risk factors. For example, people who've been exposed to nuclear radiation, for example; people who've had

prior chemotherapy for other cancers, such as breast cancer, colon cancer, lung cancer are more susceptible; people who smoke, actually, are at risk for developing forms of acute leukemia.

But I would say that the majority of time we are never able to pinpoint one specific cause. Leukemias span basically the human lifespan. There are very young infants who develop leukemia, and then there are people in their 70s and 80s who develop leukemia. So, depending upon the type of leukemia, they tend to be clustered in age. For example, acute lymphoblastic leukemia tends to be a disease of children and young adults, whereas acute myelogenous leukemia, AML, tends to be more common in older adults.

**Alicia:** And it's so important for a listener to hear you say it because we always receive the question of, you know, "What did I do to get this? How can I have avoided this?" And to your point and to your answer, no one knows; and so we always try to explain that to our patients and caregivers to, help take that burden off of them because it is the truth and it's-

**Dr. Berman:** Right.

**Alicia:** -always painful when they have that question thinking that it's something that they did or could have avoided.

**Dr. Berman:** You're absolutely correct. It is a burden for many people; what did I do to get this disease? And the answer I would say in 95% of the time, it's not known. That's a huge research question. Let me put a plug in here for the importance of sustaining research in all types of cancers, but since we're talking about leukemia today with Leukemia & Lymphoma Society, I would urge all, all of us to really try and support as best we can societies like The Leukemia & Lymphoma Society that really the aim of which is to really bring the field forward, to move the field forward. I can't stress that enough. It how we're going to make progress.

**Alicia:** We couldn't agree more. So when someone comes into your office, having shown any signs and symptoms and having explained what their situation is and you're kind of thinking of all the possible things it could be, how is CLL then diagnosed and how is it different from other types of leukemia?

**Dr. Berman:** So very good question. CLL in the United States is the most common form of leukemia. When it appears just in the lymph node, it's called SLL or small lymphocytic leukemia; and it's a common confusion in people who may have had a lymph node biopsy, for example, and the result is small lymphocytic leukemia and the doctor says, "You actually have chronic lymphocytic leukemia." So just an important terminology, CLL and SLL are basically the same diseases.

So, the disease is diagnosed by looking at the blood cells, in particular the white blood cells, in the laboratory. CLL cells will have a particular protein pattern that will distinguish them from, for example, acute myelogenous leukemia; will distinguish them from cousins of CLL like a lymphoma. So, the most important test in the diagnostic test is really from the blood and it's called a immunophenotyping analysis, also known as cell marker analysis.

For people with CLL, unlike other types of leukemias, bone marrows aren't necessarily needed. Big relief. The diagnosis can be made on blood testing alone.

**Alicia:** Thank you.

**Lizette:** And doctor how is CLL treated?

**Dr. Berman:** So, the interesting thing about CLL is that it's really a heterogeneous disease. There are a subset of people who actually never need treatment throughout their lifetime. And how this is determined is oftentimes by the characteristics of the disease at the time of diagnosis.

So, for example, a physician will do testing, again just usually of the blood, that in addition to confirming the diagnosis of CLL or establishing the diagnosis of CLL, will

also look at ancillary testing. And one important test is called a FISH, F-I-S-H, analysis which looks at DNA abnormalities of the CLL cells.

There are some DNA abnormalities that actually suggest that this may be a benign CLL and may not need treatment. There are others that suggest that this could be a high-risk leukemia and careful observation is needed. There's another test called a heavy chain gene rearrangement, immunoglobulin heavy chain gene rearrangement, which also carries with it prognostic implications. So those two tests are among the most important tests after the disease is diagnosed to tell your treatment team or provide a risk factor assessment and help your treatment team decide what type of treatment is needed.

But I would like to underscore the fact that at diagnosis sometimes treatment isn't needed, which comes as a surprise to many people and it's something that I always emphasize. This is probably among the only disease, the only leukemias that don't actually need treatment, at least initially. And your doctor or your care team will be able to review with you what the standard indications for treatment are.

I usually say there are only five indications for treatment of CLL, and that is if you have big and bulky lymph nodes that bother you. Almost everyone with CLL develops lymph nodes at some point in time. And if you remember, lymph nodes are just little nubbins of tissue that we have in our neck, on top of our shoulders, under our arms, in our groin, and they're in the middle of the chest and they line our abdomen. And the normal lymph node function is to block an infection. So, if you have a sore throat, it's not uncommon to get lymph node enlargement. Usually they're tender and small, an inch or so. And after the infection is gone, the lymph nodes, we see they go back to being not felt.

However, in CLL having enlarged lymph nodes is very common, but that doesn't necessarily indicate the need for treatment. What I tell people is, "The lymph nodes have to bother you before they bother me." Sometimes they have to be two or three

inches before people notice them. They can't turn their head easily. They have a lumpy neck. They can't, you know, work on the computer normally because under their arm there's like a tennis ball size lymph node, things like that. So that's an indication for treatment.

A second indication would be anemia or low red blood cells. That would be an indication for treatment because people feel tired when they're anemic.

A third indication for treatment would be low platelets. Platelets are those little particles in the blood that clot the blood. And if they're consistently low, that too would be an indication for treatment.

People with CLL have an altered immune system. It's not normal, and, in some instances, the body recognizes other parts of the body as foreign and wants to destroy them. We call that autoimmune or against oneself. So, people with CLL, another indication for treatment would be self-destruction of red blood cells or self-destruction of platelets. And we call that, again, autoimmune hemolytic anemia if it's red blood cell destruction or autoimmune thrombocytopenia if it's destruction of platelets.

The last indication for treatment would be if this disease changes its stripes. And this disease can morph into its more aggressive cousin called a large cell lymphoma. And that's usually pretty obvious. It's not usually subtle. People feel sick. They have low-grade fevers. They begin to lose weight. They can develop drenching night sweats. Those are all indications that the disease is on the move and usually a PET scan is recommended; and oftentimes a biopsy of a lymph node that may be hot on the PET scan will confirm the diagnosis, and we call that transform CLL and that requires a separate treatment. It's not CLL treatment. It's more lymphoma treatment, large cell lymphoma treatment.

So those are the five indications. People have big, bulky lymph nodes. People can also develop a big bulky spleen, which is a lymph node-like organ that sits normally tucked up under the left ribs and that can become enlarged in CLL. So, number one, if

you have an enlarged lymph node or spleen that bother you, if you have anemia, if you have low platelets, if you have self-destruction of your red cells or platelets, or if your disease morphs into a large cell lymphoma, those are generally the five indications for treatment.

**Lizette:** Now I know that when I was in the Information Resource Center, so we have Information Specialists that do talk to patients and to caregivers about the diseases, about their treatments, I know one of the hardest calls for me was always a CLL patient that was diagnosed, newly diagnosed, has called me and says, "I was diagnosed with cancer, and I am not getting treatment. They call it watch and wait. I call it watch and worry. I'm not comfortable with being told that I have cancer, and I'm not getting an active treatment." How do you respond to patients that may not be comfortable with monitoring or watchful waiting for CLL?

**Dr. Berman:** Right. So, combining the words leukemia and observation in a sentence is not really endearing to anybody. But-

**Lizette:** Exactly.

**Dr. Berman:** -I think with enough explanation or reviewing it enough times, and it may take weeks, if not months, to get people used to the fact that, yes, they have a leukemia but, yeah, my doctor's watching it, how can that be, it may be on day one to emphasize that there are a proportion of people, a subset of people who never need treatment throughout their lifetime. And that's something that people can really focus on that I might not even need treatment.

Not all leukemias are aggressive leukemias that need immediate chemotherapy or a bone marrow transplant; and CLL is one of them. And it takes a while, I think, for people to understand. For example, if you had colon cancer, you wouldn't want to observe that. If you have a lung cancer, you wouldn't want to observe that. But CLL is probably one of the few diseases in all oncology that can be observed and can be observed safely.

**Lizette:** And is there a reason why the person wouldn't be able to start treatment earlier? I know a lot of patients said, you know, "Why can't I just start something?"

**Dr. Berman:** So that's an interesting question. There have never been any studies that have shown early treatment is better than observation alone. That's an important feature because people do want to start treatment. People always want to be kind of on the forefront of their cancer treatment. But in this particular setting, and CLL is probably the only one that I can think of, at least in the hematology world, that there's been no study that's shown immediate treatment is any better than waiting until treatment is needed for one of the five indications that I just previously mentioned.

So clinical data, clinical studies show that there's no improvement in overall survival, which can be a normal survival if you don't have any high-risk features. And so, for that reason, oncologists are reluctant to start people on treatment if it's not needed.

**Lizette:** Right. And then the treatment actually might have side effects because isn't the treatment for CLL chemotherapy?

**Dr. Berman:** So, there are many types of treatment for CLL, and CLL has been really a disease for which the treatment has just been transformed in the last eight to ten years.

Previously, from multiple studies in multiple centers, chemotherapy, which is typically intravenous chemotherapy, was used for CLL. But starting with Dr. John Byrd's work at the Ohio University Medical Center (Ohio State University Medical Center). That Dr. John Byrd's work in Ohio was really among the first to isolate how CLL survive. What does the CLL cell need to survive? And he was able to isolate a pathway that was necessary for CLL and come up with a drug that blocked that pathway.

And that was really the huge first step for treatment. Instead of just kind of chemotherapy, which is sometimes I think of it as just like an automatic gun that just kills everything in its pathway, this is the first among the targeted pathways through



CLL. And that drug is ibrutinib, and it still remains, ten years later, one of the most active drugs that we have in our CLL treatment plan.

So, thanks to Dr. Byrd we have what we call targeted treatments. And oftentimes these are used. Ibrutinib is a pill. It doesn't mean that pills don't have side effects; they certainly do. But it sure beats sitting in a chemotherapy chair getting a needle in your arm every three weeks for six or eight months. So this has really revolutionized the treatment of CLL blocking specific pathways in this disease.

So oftentimes, and depending upon the biologic characteristics of the disease, ibrutinib can be used as first-line therapy. So what I tell people the first time that they're in the office is that we need to understand better the biology of your CLL because that way if you do need treatment, we can better plan for treatment. And if you don't need treatment, we can at least get an estimate of whether this is going to be an aggressive CLL or a quiescent CLL.

**Lizette:** And is there any space for transplants in CLL? Is, is that one of the treatment options?

**Dr. Berman:** So unlike acute leukemia, transplant has a very small role in CLL; and that is because the disease is actually how I visualize and what I tell patients is that this disease is like an accordion. And it presents, people are diagnosed with a certain amount of disease present; and over time it expands. And here I'm going to open my hands like an accordion.

With treatment, the disease then contracts again. It may not be completely eradicated because you don't need to have eradicated CLL to live a normal life, lifespan or lifestyle. And then over time the disease begins to grow again, and it needs again treatment again which, and I bring my hands back in again.

So oftentimes people respond to a visual aid such as an accordion opening and closing, and that people can understand. So, when the lymph nodes get big or people develop

anemia that's at the wide point of the accordion and then treatment usually shrinks it down again, and that response can last months, sometimes years.

So, the disease cannot be eradicated completely, at least at this time as we know it. With the newer drugs and newer drug combinations, including the targeted therapy that I mentioned, we can get the leukemia oftentimes to be really not found on detail testing. But it is too early to say, whether that type of response, which we may call a complete response, whether that is lasting. But certainly, I have followed people for many years who have a stable amount of CLL again that has never needed treatment.

So, it is a group of heterogenous diseases. Not everyone has the same disease, and that's why I usually say to people, especially with newly diagnosed disease, stay away from the chat rooms online because they're not necessarily going to be helpful for you, who you are corresponding with or writing with or whoever is writing you may have a completely different type of CLL than you do. Not, not all CLL is the same, and that's a key point in this disease. It's a heterogeneous disease.

**Lizette:** So, basically, people will have different types of side effects, different long-term and late effects from their treatment?

**Dr. Berman:** So, the side effects tend to be relatively the same. For example, with ibrutinib, a lot of people get joint pain with the drug; and it is migratory, meaning you can start if, off in your hands and then go to your wrists and elbows. And sometimes with a simple dose adjustment, the joint pain goes away. And that's a common feature.

People oftentimes can get bleeding, easy bleeding and bruising on ibrutinib; and that kind of is across the board as well.

And then there're the more person-specific side effects that some people can get – abnormal liver function tests. Rarely, people wouldn't get a rash. So those types of things are person particular.

But I'd say that when we talk to people about treatment, we generally, usually discuss the first three to five biggest, major side effects and then say not everybody gets all of these. Some people get some of these.

**Lizette:** Sure. And for you, what's the most exciting, I guess, new advancement in the field with CLL?

**Dr. Berman:** You know, there's so many. This is a disease right now that is just, really our knowledge is filling in at such a rapid pace. This is where chronic myelogenous leukemia, CML, was 20 years ago when Dr. Druker developed the first drug for that disease, again, targeted therapy called Gleevec. And that revolutionized the treatment of CML and opened up the door to understand how CML actually worked.

And that's exactly what's going on now with CLL. We are understanding pathways that the CLL cells need to survive. And once you understand a pathway, you can figure out how to block it. And that's what's so exciting right now about CLL. It's a disease that has undergone a huge transformation in treatment into actually even consider that we could temporarily eradicate the disease which we're looking at now. When I say we, I mean we leukemia doctors who are interested in CLL and are, are participating in clinical trials.

So, let me also start a new section of this, which is the importance of clinical trials. So CLL right now, hotbed of information coming out about this disease. And the only way we have learned about it is by having people with CLL participate in clinical trials. And here's another ad for The Leukemia & Lymphoma Society. You are our biggest supporters. You fund us in clinical trials. You help us. You help patients who are interested in clinical trials get to the right clinical trials, get to the right care team.

This is how the disease moves forward, and being at Sloan Kettering and have devoted my professional life to moving the leukemia field, shedding light on it, bringing in new drugs, bringing in new procedures, looking at the role of transplant, looking at the

biology of this disease has really pushed the disease forward. So I always urge people to participate in the clinical trial when there is one appropriate.

And CLL right now, the field is rife with clinical trials. So, if you are at a medical center, please inquire of your oncologist is there a clinical trial that's right for me?

And that's how important findings in the field are made.

**Lizette:** Definitely. I know that here at LLS, we really, do our best to make people aware of clinical trials and the importance of clinical trials. We do have a Clinical Trial Support Center where nurse navigators will assist patients and caregivers to find and see if there is a clinical trial that's appropriate for the patient at that time. And that it's really important, like you're saying, it's really moving the needle as to where treatment is for folks, isn't it?

**Dr. Berman:** That's exactly right. So, I think sometimes the hardest part is wading through how do I find a clinical trial? What's right for me? So, having a navigator at The Leukemia & Lymphoma Society, either online or hopefully by telephone, because not all people can use online access to Leukemia & Lymphoma Society. Having a regular old landline telephone really helps especially older people like my age who need a younger person to help navigate-

**Lizette:** You're dating yourself.

**Dr. Berman:** -including myself. So, having a navigator is a great idea. We are just beginning to have that here, which is a friendly voice when that person picks up the phone and says, "How can I help you?" there's nothing like hearing that. You know, "I've been diagnosed with leukemia. I don't know which way to turn. I've been given a huge amount of information by my doctor, all in like 15 minutes."

"Help sort it out. What do I do?" And to have someone say, "Okay, let's look at clinical trials. Let's, first of all, look at what do they do. They help find the right treatment." And all of these licensed drugs were in clinical trials. All of them had a

clinical trial that started off with, “We don’t know the right dose.” Then the next clinical trial said, “Okay, let’s see if it’s useful in 100 people.” And then the third clinical trial said, “Let’s see if it’s better than standard therapy.” So all of these drugs – ibrutinib, venetoclax, rituximab – went through that same process; and we call that Phase I, Phase II, Phase III clinical trials.

So, if you’re up for it, we’re up for studying your leukemia. That’s how I kind of look at people when they come to us. But there are people who say, “You know what, I feel like I’m a guinea pig. It’s not for me.” And I use those words myself because, a clinical trial isn’t right for everybody. It’s just not. And you, and you recognize that. We, kind of recognize that everybody has a different insight into how they want to be treated, and we honor that.

**Lizette:** Sure, Our nurse navigators usually assist people over the phone and really try to find out, like you said, if a clinical trial is something that is right for them at this time, as well as really find out what other issues that person has. Everybody is so different, like you’re saying, that even clinical trials, you know, how far is it from them? All these other things that they have to take into consideration, we do work with people to, to see if they can have, that right fit at that time.

**Dr. Berman:** If it makes sense. I say if it makes sense for you. Yeah, if it makes sense to you, if the science makes sense and if the logistics makes sense.

Increasingly, clinical trials are requesting many blood samples. And, in a way, it’s a good thing so we know how the drug is broken down in the body and whether the levels of the drug are very high or very low.

But on the other hand, sometimes you have to be in the clinic for eight hours on day one of the clinical trial of a new drug and get blood testing every hour for eight hours; and not everybody can sacrifice a day, especially in the COVID setting where we now have many responsibilities with children at home or other responsibilities. It’s not

something that can just be an assumption. Oh, yeah, I can participate in a clinical trial. It usually does require a set amount of time.

**Lizette:** Right, and like I said, we definitely tried to make sure that we talk about all these factors and really educate people on all of the expectations of a clinical trial as well as how clinical trials are really, spearheading what we are going to have in the next, you know, 10, 20 years as the new treatments.

**Dr. Berman:** I say things like penicillin was in a clinical trial at some point. No one knew the right dose. No one knew whether it worked. People just think, oh, only experimental drugs use, that's true. At that stage, they're experimental; but 10 and 20 years later they may be the pillars of treatment, and that's true for rituximab.

**Lizette:** Exactly.

**Edith:** LLS always encourages patients and caregivers to write down any questions or concerns for them to talk, for them to take with them to their doctor's appointment. Can you share with our listeners how important it is for them to openly communicate with their healthcare team?

**Dr. Berman:** Right, that's the foundation of any relationship. So, if the relationship is going to work, it has to be a two-way street.

What I teach the fellows, both by talking to them and by example, is that I take notes for the new patient who comes to me with CLL. I draw a diagram of a normal bone marrow and contrast it to a bone marrow involved with CLL. I write down words like ibrutinib or I write down words like "FISH testing" so people can look back at this as a reference.

And then I say, "Always look at The Leukemia & Lymphoma Society website because that explains it as well." I think a number of us have written background for you for different leukemias. I distinctly recall – this was many years ago, probably 20 years ago – writing a background for CML. And you still have that posted, right? And not

the original one, of course, but you do have kind of basic paragraphs for people when they're coming to look for explanations of diseases. Am I correct in that?

**Edith:** Yup.

**Dr. Berman:** Yeah, so that's very important. But I write it down for people, and I write down the different medications, and I write down the first few important side effects, so people have that as a reference. Not everybody has a computer to get to The Leukemia & Lymphoma Society website.

I think to have a reference like that is important; and I also think simple things like writing down the name of the care team or the name of the people taking care of you, whether it's the secretary who answers the phone or the nurse who answers your question so people feel that they're part of a larger family of caregivers.

So, that's kind of how I look at communication, that it's an introduction to a medical family so to speak and that names should be used and information written down and access to information. I think education dispels the dark mist of fear; and I think it can only do so if people understand what they have and understand the treatment approach, which is sometimes for CLL no treatment, at least initially.

**Edith:** Very well said. And can you tell us a little more about some common questions you hear from patients?

**Dr. Berman:** Oh, so one is, the first question is how did I get this; and the second is, is this communicable? And the answer to that is interesting for CLL because there are families in which many members of the family have CLL, brother/sister, mother/son. We have a couple families that appear to have this in common; and we can't tell why, but I would say that's present in only 3% of people or so or even smaller who have CLL that there's a relative.

So that would suggest that there's something in the environment that may trigger CLL, and if so, what is it? And we really don't have any answers for that.

**Edith:** For those of you who would like printable questions, please go to [www.lls.org/whattoask](http://www.lls.org/whattoask). And you could also find the link listed below this episode on the episode page. Thank you very much, doctor.

**Dr. Berman:** You're very welcome.

**Alicia:** Doctor, is there anything that we didn't share today that you think would be important for our listeners to hear?

**Dr. Berman:** Having something like The Leukemia & Lymphoma Society online and available to anybody like the doctor in a small town is a great asset.

**Alicia:** Such great advice. Thank you so much for joining us on this episode to discuss chronic lymphocytic leukemia and sharing such great advice. And thank you also for everything that you do for patients and their loved ones. It's been so great speaking to you today.

**Dr. Berman:** Well, it's been my pleasure to talk to you all, and I'm going to say the same thing. Thank you for what you do.

**Alicia:** For those listening who would like to learn more about leukemia, you can visit [www.lls.org/leukemia](http://www.lls.org/leukemia). And for those who'd like to order our free booklets about CLL specifically, we encourage you to visit [www.lls.org/booklets](http://www.lls.org/booklets). Thanks so much for listening.