**Understanding Chronic Lymphocytic Leukemia (CLL)**

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**SPEAKERS**

Dr. Chris Hillis, Dr. Bill Evans, Narrator

**Narrator** 00:00

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**Dr. Bill Evans** 00:22

Welcome to the Cancer Assist Podcast with your host Dr. Bill Evans and today we're going to be talking with Dr. Chris Hillis about Chronic Lymphocytic Leukemia (CLL). And before we get into our conversation, I just like to remind our listeners that the Cancer Assist Podcast is brought to you by the Cancer Assistance Program here in Hamilton, Ontario. The Cancer Assistance Program provides a variety of free services to cancer patients, including free rides to the Cancer Centre and to medical appointments, equipment, loans and nutritional incontinence supplies amongst a number of other supports for cancer patients. And these podcasts are made possible by generous donations from individuals in the Hamilton community with a hope that by learning more about cancer, its causes current best treatments and the supports that are available in our community, it will make the challenge of dealing with cancer and just a little easier. So welcome Dr. Hillis. I'm delighted to have you here on the podcast today. You bring a lot of knowledge and experience of a chronic lymphocytic leukemia, which I think our listeners will benefit from. Maybe, just to start, maybe tell us a little bit about yourself as a hematologist who treats at the Cancer Center. How did you end up choosing this as a career?

**Dr. Chris Hillis** 01:34

Yeah, thanks. Thanks for starting off easy on me. That's a question I know I can answer. And thank you to the Cancer Assistance Program for having me. My initial education was actually in cell biology. And so I think that would be very natural going into hematology, because all we talk about all day are individual cells that are floating around in the blood. Towards the end of my undergraduate degree, I had a career selling hot tubs. And at that age, the hot tub commission was very lucrative. It felt like a lot of money. And I thought that was going to be my future. But I had a very wise professor who saw that I, you know, had some capabilities in science and that and sort of steered me away from that and said that he thought an application to medical school was probably wiser with my grades and aptitudes than running off to sell hot tubs now. Noble career, of course, in hot tub sales, but but that really did steer me towards medicine. And really, it was good mentorship that brought me towards hematology. There's a couple of notable people who I've met along the way. So Parveen wasI, who's an assistant dean at McMaster University was my guidance counselor, as it were in medical school. And she really taught me about hematology and her passion for hematology is what got me interested. Then as I moved through my internal medicine and hematology training, it was meeting someone who's now a good colleague, Dr. Graham Fraser, who's a world expert in CLL. And he took me under his wing. And that's how I got interested in CLL, specifically, and doing my fellowship training with him. So a bit of good luck for a professor you know, saying medicines a good career, although I think I would have been very happy as a hot tub salesperson, and then good mentors along the way.

**Dr. Bill Evans** 03:20

Well, I'm sure there are a lot of patients that are grateful that you chose medicine and not hard times, although there's probably some disappointed people out

**Dr. Chris Hillis** 03:27

there. Don't have a hot tub now. Yeah, exactly. So

**Dr. Bill Evans** 03:31

then you focus down because there's a lot of hematologic issues, you know, from just anemia is and sickle cell disease and all sorts of interesting aspects of hematology, which ended up in CLL. And that's it's because of grant Fraser's influence wasn't. Yeah,

**Dr. Chris Hillis** 03:47

so I my my fellowship training was in two disease sites, so CLL, and another group of conditions called Milo proliferative neoplasms. And the two things that those conditions share is that the patients come in with very high levels in their blood, other areas of Hematology focusing on very low levels. So I always joke that I'm the high blood count guy. So if you have a high hemoglobin or a high white blood cell count, that's not acute leukemia, you're going to get into my clinic for that. So my fellowship training focused on both of those disease states because the treatments well different, are lifelong anti cancer therapy, often oral. And so what my clinic often focuses on is the management of patients who will live with hematologic malignancies for a good portion of their life, in some cases, many decades. And so the issues that we're focused on in my clinical practice are not just about the acute needs of undergoing cancer therapy, but how you manage your cancer therapy in combination with other diseases you may get over life. So now you've got CLL and high blood pressure, or you have an NPN and you've had a heart attack, and how do we wed together your chronic medical care? conditions with your chronic hematologic malignancy. And that's where my research focus actually is as well,

**Dr. Bill Evans** 05:06

that's very interesting, I hadn't really thought about then the length and how the strategy and approach of an oncologist has to be very different perhaps from what I had to do as a London oncologist where you're very much focused on a more truncated a piece of life, shall we say, then, then the long haul of several decades. And that's certainly true with CLL, because the natural history of the disease is quite lengthy, and modern treatments are making it even longer. And so that changes the whole dynamic of what you're dealing with CLL is pretty common. I know that just in preparing for this podcast was about 2200 new cases of, of CLL in Canada each year. So it's not rare. And of course, those people are living with their illness for substantial periods of time. So I don't know what the prevalence figure is. But that does mean there's a lot of individuals out there with, with CLL. And, you know, maybe we should just talk about a bit about how that disease, what it consists of how and how it manifests, so that our listeners have an idea of how a person might present with it, because it isn't always something that's kind of acute, but it might just be picked up on a routine blood test. Right?

**Dr. Chris Hillis** 06:18

That's exactly right. And I think it's important to talk about diseases like this, because there's not a lot of public awareness about cancers that can be found totally asymptomatically. And often, as you said, by accident, so the vast majority of patients who I meet with a new diagnosis of CLL, it really is what we call an incidental finding. So they're having a test for some other reason. And they happen to notice that the white blood cells are higher than they ought to be. White blood cells normal job in our body has to be our immune system. And so when those are high, the thinking is often that there's some immune system thing going on, have you had an infection, are you reacting to something else, or they may have an imaging test, a CAT scan, and X ray and ultrasound and those show swollen lymph glands, lymph glands being the master command centers of our immune system. So if you have CLL, which is ultimately a cancer of immune system cells, they're going to be wherever your immune system is, in your blood, your lymph glands are a big lymph gland called the spleen, which lives under your stomach. And so if people have symptoms of CLL, at the time of diagnosis, which is actually the exception, it's quite rare to have frank symptoms at the time of diagnosis. Because as we all know, in modern medicine, we get a lot of tests. You know, you go to your family doctor for your diabetes, or high cholesterol, you're getting a blood test. And included in those blood tests are often a blood count, which is what we can diagnose CLL from, or you might be getting a mammogram as part of routine screening for breast cancer. And on that mammogram, we see that there's lymph nodes in the armpit. And so these are the common ways that CLL is found. So people come in, totally shocked, unfortunately, because they were going for something else, and now they have cancer, and they probably felt fine to it. Yeah. So it's very different than if you're going for a mammogram, which is very distressing and anxiety provoking, of course, and they find a lump that gets a biopsy, and now it's breast cancer, you at least know that's why you are going for that test, where if you're going for a blood test for your diabetes, and now you've been diagnosed with a blood cancer, that's that's a different kind of surprise or shock. And then

**Dr. Bill Evans** 08:27

I mentioned the just the terminology leukemia, I think to most people, that conjures up an image of something rather acute, like they've heard of, a lot of people have heard of acute leukemia, and maybe associate that with rather of fulminant disease and a poor outcome.

**Dr. Chris Hillis** 08:41

Absolutely. And if you think about movies about young children who are dying of cancer, it's often acute leukemia. And so what people know about leukemia from mainstream information is acute leukemia and acute leukemia as a medical emergency. It requires treatment right away, people are hospitalized for a month or longer to get that treatment. And so you go on Google when you hear the word leukemia, and that's what comes up. And so the first thing I say, when I meet people almost always is we're going to focus on the See of CLL, which is chronic, not on this, the second Dell, which is leukemia, because leukemia simply means white blood, that is all it means. So if you have high white blood cell counts, because of acute leukemia, you've got white blood, if you've got high white blood cell counts, because you have too many lymphocytes, which is chronic lymphocytic leukemia, still white blood,

**Dr. Bill Evans** 09:30

maybe a brief little digression here, and we talk about white cells, but there are more than a few types of white cells and not to get too deep into the weeds. But it might be helpful just to explain the major types and a little bit about what they do what their function is, because that becomes important in CLL because we got too many of a particular type of white cell, but they don't function normally. And that can produce some of the problems downstream that these patients may encounter.

**Dr. Chris Hillis** 09:59

Yeah, So we have a very sophisticated immune system, humans have definitely got a very complicated interplay of things working to keep our bodies safe from infections and even cancer. So one of the rules of our immune system is to fight off cancers as they develop in our body. And so we have a few different things floating around in our blood white blood cells whose job are to, to provide protection against invaders that come into our systems. And so what has really helped my job is COVID, people have a better understanding of the immune system than ever before, because they're wanting to read about things like vaccines and how vaccines work in our body and what are COVID antibodies by have too many or too few. So lymphocytes, which are the cells that become cancerous and when you develop CLL, we have two main types, we have B lymphocytes, and we have T lymphocytes, T lymphocytes we may know about because for folks with HIV, that's they get too few that's toxic to their T lymphocytes, so that part of their immune system gets very weak. For B lymphocytes, their main job in our body is to eventually produce antibodies. So you get a COVID vaccine, you get, you see a little bit of a protein related to COVID, the immune system starts making antibodies to that. And it's those B cells doing that work. And so in CLL, it is it is those B cells that were our body is making too many of and that's where you develop CLL. The other cells of the immune system that float around in our blood are a little bit dumber, they don't necessarily have a specific job, like I'm going to fight strep throat, or I'm going to fight off COVID Or influenza or something like that. They're just your foreign, your bad. Let me get rid of you. And so those are things like neutrophils and that where they just say this is wrong. Let me see if I can kill you off.

**Dr. Bill Evans** 11:52

That's a great explanation. And I also was kind of surprised to hear a positive out of COVID. I hadn't thought there were too many.

**Dr. Chris Hillis** 12:00

Do you try and do what you can right?

**Dr. Bill Evans** 12:04

Now you have too many. But when's it too many? What's What are you looking for what sort of defines too many when someone has a blood count? What's Is there a number

**Dr. Chris Hillis** 12:13

that no and that that that's that's very distressing to individuals to hear. And so because CLL is a very chronic very slow moving condition, it unfortunately is not something that we can care. It is something that folks, once they've been diagnosed with, it will live with it for the rest of their life, we can using treatments that we'll talk about, get it into a very quiet state of remission, where we can't see any evidence of the CLL. But unfortunately, there's a few of those CLL cells sleeping somewhere in that individual's body, and they will, they will rear up again. And because of that fact, and because people often will come in not feeling sick from it or having symptoms from it. We know from many studies that we've done that racing into treatment will actually just give people side effects longer than making them live longer with the quality of life that we would want them to have. And so while the white blood cells will continually rise year after year, we actually ignore what the white blood cell count is. And so if a normal amount of lymphocytes in our body is somewhere around the two to four range, people will get diagnosed maybe with 15. And that can be very alarming because it's three, four or five times normal. But but that doesn't matter, because these are very small cells. And if they're not bugging them, we don't bug the cells. So if it's not bugging you, I'm not gonna bug it as what I will often say to folks, it's when they start to build up and cause symptoms or other abnormalities in the bloodwork, then we will start treatment. So it's a bit like real estate, location, location, location, they've built up in a lymph node, like the spleen that we talked about earlier, and it's pushing up against the stomach. So if somebody's getting full really quickly, and they're losing weight, because they just can't keep up with their nutrition, then we would start treatment. But we can have folks walking around with blood counts of three 400 feeling nothing. And it's really only if they start to build up in certain places and cause symptoms that we would then start treatment. And so I always joke with patients, you know, when you're looking at your blood counts, put your thumb over the white blood cell number and just read the rest, because that's what I'm doing. Because they can as long as they're not making the other blood numbers go low, we're not going to start to ask

**Dr. Bill Evans** 14:27

about that because they're coming out of the bone marrow when you're getting too many of them, then they're going to crowd out presumably so simple way of thinking about it hard to understand fully the dynamics in the bone marrow, but if you get too many lymphocytes there, then the cells that make red cells and the cells that make your platelets to make the blood more sticky and able to clot. Those can start to fall, right?

**Dr. Chris Hillis** 14:50

Yeah, exactly. So the bone marrow is the factory where a blood is made. And so there's machinery there to make red blood cells which carry oxygen around our body. There's machinery there to make platelet to stop us from bleeding when we cut ourselves. And then there's the machinery that makes white blood cells that the immune system that we've talked about in different machines, depending on the type of white blood cells that are being made. And so over time with CLL, that factory just gets taken over by those machines making lymphocytes, which crowds out everything else, making all the other healthy stuff. And that would be a reason why we would need to start treatment.

**Dr. Bill Evans** 15:25

But those machines must be in some way broken because the lymphocytes they turn out aren't normal lymphocytes, right? They're, they're abnormal in some way. And I guess that gets us into some of the special tests that you do when you're investigating a person with CLL. Because there are changes in the DNA of those cells, which probably ultimately translates into them not being effective as antibody producing cells, when they're when the patient is confronted with a with a viral intruder or something of that nature.

**Dr. Chris Hillis** 15:56

Yeah, so the CLL cell itself starts off as one misbehaving CLL cell, it divides and makes two that divides and makes four to eight to 16, and so on, until you've got trillions and trillions and trillions of these CLL cells in your body. And so that is a clone. So it all starts with one cell. And everyone else that we see in the blood is a, you know, a twin to that original cell that decided to misbehave in that person's body. And the next question we'll ask is, well, why did decide in their body? And I'll just answer to say, I'm not smart enough to know that. And we don't have the good research about why this person and not their neighbor or not their sister, that debt got CLL. But we do know in them that it is, it is a single clone, so that the testing that we do to diagnose CLL is to say, all these lymphocytes that are floating around in the blood, they're all the same. And so we look at the surface of those cells for particular markers to say, yep, you've got, let's say, 15 lymphocytes floating around in your body, and 10 of those all are lambda lymphocytes. Well, that will tell us that they're clonal, they all come from the same parent, and thus is is CLL. So it's diagnosed on a blood test. If there's only enlarged lymph nodes, it would require a biopsy to diagnose it because the CLL cells haven't gone into the blood yet. They're just hanging out in lymph nodes. And that would be the example that we gave earlier about the mammogram where you see that somebody has an enlarged lymph gland in their armpit, get a biopsy, which is a needle test, where we take a piece of that lymph node and we see that there CLL cells in the lymph node, the same sort of staining process that we would do on the cells in the blood to diagnose it, just it needed a biopsy.

**Dr. Bill Evans** 17:43

Do you need to do a bone marrow and all patients are no, no, not at all? No,

**Dr. Chris Hillis** 17:47

the the diagnostic process doesn't involve a bone marrow unless there's something not quite right about what's going on. And we just want to be extra sure that, that we've got the right thing that we're dealing with,

**Dr. Bill Evans** 17:58

though CLL differs from patient to patient to patient in terms of some of those molecular changes in that clone, it's gone wild. Slowly wild, I guess, because this isn't a rapid process. It's a slow process, for the most part, isn't it? And, and some of those abnormalities can predict whether you're going to have a better outcome than not right. So tell us a little bit about some of those molecular changes. And I think a lot of listeners these days, who certainly those who have CLL often know, a good deal about the disease. So, you know, I think we could be fairly sophisticated about talking about deletions of parts of genes and so on here.

**Dr. Chris Hillis** 18:45

So I'm thrilled to be nerdy at any time. So I'm glad that we have this opportunity now together bill to nerd out for a second or two. So I mean, I think we can all agree that the blood is the coolest part of the body. And when when people how the lungs are, okay, well, look, are you to disagree on that? You know, I think that the reason why CLL is a different disease is that while we can have lymphocytes in our body that all look the same, where they are in their life journey is actually different. And where the CLL cell develops in the journey of a lymphocyte actually depends on the behavior that it will have as a cancer. And so as you mentioned, the factory where the blood is made is in the bone marrow, blood cells leave the bone marrow and they go to the different parts of our immune system, and that depends on our age where they might go. So there's something called the thymus, which is very important in T cell development when we're young children that goes away when we're adults. But that's where the immune system cells really grow up is in the periphery of the body. So the outside of the bone marrow, parts of the immune system like lymph glands and that and so an immature lymphocyte will go off to the lymph plan to grow up, that's where it will get exposed to viruses, bacteria, other things and become a very focused part of our immune system. And the way that that is accomplished within the CLL cells itself, or within a lymphocyte itself, which could then become a CLL cell is a process of mutation. And whenever we think about cancer, we we have to think about mutation because mutation is what is required in order for cancer to develop. So that's the DNA in a cell changing, so that the cell can become smarter than the things in our body that protect us from getting cancer. So avoiding the immune system, the ability to grow rapidly, the ability to develop a blood supply, would be three examples of things that are required in order for something to become a cancer cells to become cancerous. And that all starts with mutation. In our immune system, we normally have mutation, it's the part of our body where mutation is allowable. And it is the mutation of the DNA in our immune system cells that allows us to fight infection. So a cell may go along and try and fight off a virus, and it doesn't do that great of a job. So then it will mutate to get smarter at fighting that virus. And so that's a process where the cells go through somatic hypermutation and otherwise, to develop a specificity against certain things that attack our body. And so there's immature lymphocytes that haven't done that. And then there's mature lymphocytes that have done that, and CLL can develop in both pools of that. And so people will talk about the IG H V mutation status, which is a risk factor. And so the unmutated cells, which is the one that hasn't grown up yet, those ones don't respond particularly well to chemotherapy, where if you have a mutated one, the one that has grown up been exposed, the DNA has mutated, those do respond reasonably well to chemotherapy. So you can have two people who look like they have the exact same disease, but then we do the IG HV mutational status testing to see are they from the pool that hasn't grown up yet, or the pool that has grown up, and we know that they would, those two different people would respond very, very differently to treatment.

**Dr. Bill Evans** 22:16

And then there are other mutations 17 P and the 13 P deletion and cube deletion Sorry, we don't need to go that deep. I don't think with our listeners. But just to give the idea. And I really loved your nerdy explanation of the mid maturation and how mutation is a natural process in order to adapt to the pathogens that lymphocytes are meant to attack, because we know they're mutating out there, the virus and so on. That's how we ended up with COVID-19. And they have to adapt in order to be effective against these new things coming into our system. But the important part here is that you have tests now that will allow you to differentiate these different subtypes of CLL is not just one disease, and that has prognostic significance. But as you just said, it makes a difference to the therapy you're going to choose for the patient, which is, is tremendously important. Maybe just before we talk about therapy, one thing I meant to ask you about and forgot or are there any specific things that increase your risk of getting CLL people always want to know about risk factors and we smoker, this this exposed to radiation spent too much time on the beach, any of those kinds of common things that we associate with certain types of cancer relevant and CLL? Or is it just something that comes out of the blue?

**Dr. Chris Hillis** 23:32

Yeah, unfortunately, there's nothing that we can say if you stop doing this, you won't get CLL, we don't have that tight of a link to any risk factor. Unfortunately, with CLL, there are associations and so being a firefighter, for instance, is associated with developing CLL. And that's over a, you know, 30 or 40 year career, I think putting out your backyard fire wouldn't count as as that, but, but certainly the career of being a firefighter has been associated with it. And I mentioned a comment earlier about not knowing about your brother or sister getting it seems to run in families. But there's not a genetic predisposition that we have found. And so if your brother or sister has CLL, or your mom or dad had CLL, you are actually more likely to develop CLL, than you would just in the general population, not by an alarming amount, and not by so much that we actually suggest that siblings get tested and children get tested. But just an observation that has been noticed in population level studies. And whenever you hear something like that, it does make you wonder it's that nature or nurture thing. Is there something in your DNA that you share with your relatives that led you to get CLL or because you all grew up in the same spot and had the same environment. Is there something there and we just don't know, unfortunately?

**Dr. Bill Evans** 24:53

Well, before we dive into discussion of treatment, why don't we take a short break for a message from the cancers This is program. And we'll be right back with Dr. Chris Ellis to talk about treatment for CLL.

**Narrator** 25:07

We'd like to take a moment to thank our generous supporters, the Hutton Family Fund and Banco creative studio who make the cancer assist podcast possible. The cancer Assistance Program is as busy as ever, providing essential support to patients and their families. We remain committed to providing free services for patients in our community, including transportation and equipment loans, personal care and comfort items, parking and practical education. These services are made possible by the generosity of our donors through one time gifts, monthly donations, third party fundraising, corporate sponsorships, and volunteer opportunities. Visit cancer assists.ca to see how you can make a difference in the lives of cancer patients and their families.

**Dr. Bill Evans** 25:51

We're back with Dr. Chris Hill is talking about CLL or chronic lymphocytic leukemia, and we were just about to dive into treatment. Maybe just before we do, we didn't define the population that's most likely to show up with CLL from one of those tests for their diabetes or their heart failure or something. I mean, we should talk a little bit about age and gender and and then anything that would drive a clinician to start treating sooner because this is such a chronic disease, but

**Dr. Chris Hillis** 26:20

typically a disease of people into their 70s when they're diagnosed slightly more men than women get diagnosed with CLL. But certainly most often a disease of people in the 60s 70s 80s when they get diagnosed, certainly I have patients in my practice of all ages, I think it would be case reportable to have pediatric cases of CLL. But but certainly not impossible. From a treatment point of view and some of the factors to the second part of your question. The first treatment is what we call observation. It's also called watchful waiting. And that's a very stress provoking treatment. Because when you're diagnosed with cancer, you think about what you know about cancer, which is we cut it out, we give it chemotherapy, and we give it radiation. That's what people know, from their loved ones or from media or what have you about the treatment of cancer. So when they come to see their Hematologist Oncologist to talk about a new diagnosis of CLL. In their minds, the individuals are often preparing to get started on treatment. And what will sometimes say is you're doing great, your numbers are fine. You don't have any swollen lymph glands will see you back in a year,

**Dr. Bill Evans** 27:28

which is like, gosh, or abandon me Exactly,

**Dr. Chris Hillis** 27:32

yes. And so you know that that's very, very difficult to get your head around. And I totally appreciate that. Because what we know is that if we race in with treatment too soon, we don't benefit folks in the long term from that we just expose them to the risks of treatment without them benefiting from it right yet. And so we have indications for treatment, and through that watchful waiting period, that is treatment, we're watching the folks and observing for particular indications for treatment. And the reasons why we would do treatment is is broadly defined as the patient has symptoms. So there's some sickness or illness or reason why they want treatment. And, you know, my biggest goal in my career, I think, is to perfect the crystal ball, so that I know the day before it's going to make them sick. Because I'd like to maximize that watchful waiting observation part. You know, I'm not saying our treatments are so toxic that you want to dread treatment, we can usually get people through treatment without too much difficulty. But it would be really nice to balance that maximizing off of treatment, but not getting to the point where you're feeling too beat up by the disease. And starting on treatment and more of a hurry, because one in five people who get diagnosed with this actually never need treatment, they only have the observation, watchful waiting stage, and then we'll pass away from a different condition. And so when it fits the four and five that we then, you know, ultimately we'll go on to treatment. And the reasons for treatment are just what I said symptoms. So low blood counts, so the lymphocytes have crowded out that bone marrow, so the factory's not producing the other parts of the blood, we would need to institute treatment for that. lymph glands become quite swollen or symptomatic, and the textbooks would allow lymph nodes to get up to 10 centimeters before we could start treatment. So you can imagine in your neck, if you had a swollen gland that was 10 centimeters or two up your, it would be correct. Yes, exactly. Joking. If can't check your blind spot because of your lymph node, it's probably time to start treatment. And so that the spleen we've already talked about if that starting to bug people, we would initiate treatment. And then the really interesting thing about CLL and probably frustrating for folks who have it, is that because it's a cancer of the immune system, it can cause the immune system to do some pretty wonky things. And so the immune system can actually start destroying parts of the body and the most common thing that the CLL thing wants to do is destroy other parts of the blood and so it can make the red blood cells or platelets low not because they're not being made, but because the antibodies being produced by these lymphocytes have gone on and decided to get rid of the red blood cells and platelets. So if we can't get a handle on that, with treatments like steroids, which calm the immune system down, that may be a reason why people would need to start on treatment. And then finally, patients will experience immune system symptoms as well not just the destruction part of things, but saying, hey, my immune system is revved up. So fevers, and that would not just be getting a fever for a weekend, if somebody has a fever for a weekend, they probably have an infection. But if they have a fever for more than two weeks that we otherwise can't explain. If they lose more than 10% of their body weight in six months, or if they have drenching night sweats. So not just do a bit of dampness around the color, I'm actually changing my bed close, or bed sheets through the night. Those are what we call the symptoms. And those are common in lots of hematologic malignancies, but that will tell us that treatment is something that needs to be done. And so when folks have any one of those things, or combination of that, that's when we end the observation period and move into the period of active treatment. So

**Dr. Bill Evans** 31:16

that's very helpful. And as we move into the active treatment, I'm sort of almost overwhelmed by the changes that I've seen over my career, because when I trained, we back at Princess Margaret Hospital, we only had one drug, and what we call an alkylating, drug chlorambucil. And it's still around and still used I understand in some circumstances, but I think thinking is evolved and the available medications to treat CML have changed radically, and maybe paint that journey and where it's got his to now because I think it's quite fascinating. It's just one of the many, many hopeful advances we've seen in the treatment of malignant diseases is to see the number of agents that work by sophisticated mechanisms to control a malignancy like CLL. Yes,

**Dr. Chris Hillis** 32:04

exactly. So yeah, same thing. When I started my career, the vast majority of patients were getting treated with some form of chemotherapy and chemotherapies job is to stop cell division largely, or to interrupt cell division in some sort of way to slow down those rapidly growing tumors. That doesn't work particularly well in CLL. Because CLL is a very slow moving condition, there's not a lot of cells dividing at any given time, which is often part of the requirements for standard chemotherapy to work as it would in other malignancies. And so very, very brilliant people have been doing drug discovery, like what you talked about to try and to mock up cell division for CLL cells or to, you know, get rid of CLL cells in another way that doesn't require cell division necessarily. And as we have developed these new agents, and tested these new agents at the Juravinski, we do a lot of CLL research, we've learned that there's not a one size fits all approach. Even though we've developed some pretty good treatments, we apply them to different types of CLL. And so our discussion around the special genetic tests that we do to define the type of CLL someone has, is now incredibly important, before we had the test, but nothing we could do about it because we had one or two treatments. So we knew the disease had perhaps a less favorable prognosis. But we didn't really have anything that we could action, we just could tell the patient Well, unfortunately, you're not going to do as well as somebody who doesn't have this risk factor. Now we actually have things that we can do and apply a personalized type treatment approach for individuals. And so we do the risk testing at the time treatment is needed. And I think that's a really important message. Because when folks who maybe are listening to this, we've just been diagnosed with CLL or recently been diagnosed with CLL. They're going to say, Do I have deletion? 17 p 13 que mi mutated or unmutated. And if they go and ask their oncologist or hematologist that their answer is going to be I don't know, because I didn't look. And we only look when treatments needed, because it can actually change over time. And so you may not have deletion 17 p when you're diagnosed, but you may at the time that start to you know, because it can take 15 years before you need treatment. And so things can evolve in the CLL clone itself, and additional genetic abnormalities can come come along. And so we test those things at the time treatment is needed. So we have the up to date information for treatment decision making, not what happened five or seven years ago when you are diagnosed, for example. So we take the genetic information, which is the how risky is this low risk, intermediate or high? We think about that. And then we look at the person sitting in front of us and have a conversation with them. What's their function like? Are they frail? What are their values? What's important to them at this time? Is it you know, quality of life being Get home, is it okay to come back and forth to the cancer center a lot for treatment, because really where we're focused right now, and where it has evolved to is to notions of treatment, time limited or continuous. So time limited, you go on a treatment for a year. And then you go back into observation or watchful waiting for a continuous treatment where you take a few pills every day, and you continue on that treatment for a few years, well, it's working, so you're continually on treatment, till the CLL, creeps back up on us again, and then you switch to your next treatment. So very different paradigms of treatment. And most patients, you know, can be considered for both of those. So it really has to be a discussion because the time limited treatment is very, very busy in the beginning, lots of trips to the cancer center bloodwork and fusion clinic visits, where the other one is you get, you know, your bottle of pills, you go home, you start taking them, and you come to see us every few weeks in the beginning, and then every few months after that. And so if you're working, if you've got a young family, you may have a different different preference. And then of course, side effects, every every treatment, of course comes with a list of side effects, we only have to watch American TV for five minutes. And the commercials, we realize that the you know, the long list of side effects is there for everything. And some of the agents have side effects which say, hey, if you've got this medical condition, maybe this isn't the right treatment for you. One of the class of medications that we use is called a BTK inhibitor, and those increased the risk of bleeding. So if you're on medication or another bleeding condition, let's maybe avoid those at first, we may need them down the road, because we've got other treatments that don't have that side effect. And so it may be better to use that for that individual.

**Dr. Bill Evans** 36:48

And there's a member in that class that can increase your risk of having atrial fibrillation and have a heart condition have different rates of different rhythm to your heart. So that has to be taken into consideration. There's a lot of factors and being weighed. But if I was very interested in the continuous versus the intermittent therapy, I also noted in reading that there seems to be a move to you to move away from what we call the alkylating agents speak and chemotherapy agents, not just for side effects, but because they thought that they may be induce more mutations and maybe also depress the bone marrow and make it harder to introduce other therapies in the future. So are we moving away from the chlorine puzzles and and into the BTK inhibitors and so on?

**Dr. Chris Hillis** 37:33

Yeah, so the challenge always with doing podcast is that it reports records your opinion on a day and time. And so I wish I reserve the right to change my opinion on this as the science evolves, and of course, and so we talked earlier about unmutated versus mutated where in the journey that lymphocyte became cancerous or developed into a cancer cell in the person's body. And I think we can pretty confidently say in the unmutated patient population, we will not use calculators or other traditional chemotherapy agents anymore. We know that in that patient population. It just doesn't work as well as novel agents. The more common for younger patients combination of chemotherapy drugs was fludarabine and cyclophosphamide, also reasonably old drugs as well now with a with a molecule called rituximab, rituximab is actually an antibody, sorry, that tricks the body's immune system into fighting off the CLL cells. So it looks for a marker on the CLL cells and targets that that cell for destruction by the immune system. And so we were very commonly using a combination of drugs called fludarabine, cyclophosphamide, and rituximab. And for the mutated patient population that can almost be a functional cure. There are patients in the clinical trials of fcr, who have lived without any evidence of CLL for longer than 15 years, which was never seen before. And really, it's in that mutated patient population. But as you mentioned, there's their side effects that go along with that and the potential for long term damage to DNA and other parts of the body that give us pause in using that in that mutated patient population. I think we're seeing a shift away from traditional chemo immunotherapy. That's what we call fcr as a class, but there are still a few patients where it might be right for them in 2024. I don't really use it a lot, but there may be the odd patient too, if we look at their factors there CLL and that we may say, Oh, this, this still might be the right choice for you. But by far and away and definitely for unmutated and higher risk disease. We're using BTK inhibitors and there's a few available in Ontario and in Canada right now to choose from, or the time limited option which is a combination of medications called vanetta clacks and Obinna tuza map Obinna tuza map is the newer generation of rituximab works in the same way but works more strongly than rituximab does.

**Dr. Bill Evans** 40:08

So I'm hearing great deal of tailoring of treatment to the specifics of the person's lifestyle, age responsibilities, as well as the biological features of their cancer. So it's really got to be quite sophisticated how you make the decision to treat and to treat with a particular regimen?

**Dr. Chris Hillis** 40:27

Well, I'd say, you know, as I, as I, my patients, after listening will know, I always joke with them, they made me go to university for 14 years to figure this out. And so I'm getting my money's worth on that one, because it certainly has become very complicated.

**Dr. Bill Evans** 40:40

And it can be expected to become more complicated, I think, based on the research that's going on. And I want to do, I do want to talk about research, because you mentioned clinical trials a minute ago. But just before we get there a couple of other things about the illness, we talked about how the immune system is not functioning appropriately. And he talked about overdrive, but there's sort of underdrive too, I guess, in terms of producing antibodies against certain pathogens. And so these individuals can be at higher risk. And I think there's some improvement, doctors have to be alert to certain rare infections. And maybe there's some preventive measures that you can also use to help a patient stay free of infections, maybe talk a little bit about that. Yeah,

**Dr. Chris Hillis** 41:24

happily, I think there's, there's a lot more to CLL, beyond just selecting the right medication to treat it when treatment comes up. And so what you're talking about applies not only to the treatment, the active treatment phase of the disease, but the watchful waiting phase of the disease. And so the CLL cells are made very, very rapidly, and they're not necessarily as smart as other lymphocytes in the body. And they're also taking over from other lymphocytes being made the normal lymphocytes who would help you fight infection. And so folks with CLL, either at diagnosis or over time, will have low levels of antibodies floating around in their blood. And we need antibodies to float around into our blood because when an infection comes our way, they'll recognize that infection from when you had it before and say, Oh, hey, you're influenza, I'm gonna mark you for destruction or you're a strep bacteria, I'm gonna mark you for destruction, because your body's seen that before. Or better yet, hopefully, you've had an immunization before. And the immunization has developed antibodies in your body that can then clear the infection from even happening. And so in general, the antibody levels across the board just become low. If patients end up with a quite, you know, significant infection, we will then start to replace antibodies for those individuals, you know, if they, if they get the flu or something like that, it's not necessarily a reason to get started on antibody supplementing therapy. But with a significant infection, we will then start them on a program that's an under the skin injection that's done at home over 15 to 30 minutes, once a week. So the patients do that themselves. And that's to prevent, you know, very serious infections from happening again. Because when your immune systems low, you can develop more rare or weird infections than the run of the mill pneumonias and things like that, you may get a fungal pneumonia, for instance, as opposed to a bacterial pneumonia, which would be much more common. The other thing that our immune system is very important for besides fighting off infection is fighting up cancer, it recognizes cancer cells as foreign and destroys them. And so if your immune system is not working particularly well, unfortunately, you are at a higher risk of other cancers. So folks living with CLL do carry an increased risk of other cancers, the most common one being skin cancers. And so T cells are very, very important for fighting off skin cancers. And if you've got nonfunctional lymphocytes on the other camp B cells, or just B cells that are crowding out your healthy T cells, you're not going to be as fortunate to have that robust immune system to help you fight off skin cancers. And so we recommend that folks with CLL get an annual skin exam now we can all look at the front of ourselves, but we need somebody to look at the back doing yoga in front of the mirror doesn't cut it, we really do ask that they go to a medical professional to to have that done. You know, we have to remember for CLL patients, it's not only the infection fighting part of their immune system that needs to be paid attention to but also the cancer fighting part of their immune system. So while everybody should get their age appropriate cancer screenings, pap smears, mammograms, you know, the FIT test all of that, definitely this population, we remind them time and time again. And the last thing I'll say is okay, so your lymphocytes aren't working that well. Your antibody levels aren't that great. Should I still go and get my flu shot? Yes, definitely. Let's get as many functional antibodies in your body as you possibly can. Even if your response isn't going to be as much as somebody else's. That means that you won't be able to find it as well, if you were to get it, so let's give you a leg up by getting those vaccinations that are recommended. Well,

**Dr. Bill Evans** 45:06

I'm getting educated here, I wasn't even aware of the risk of skin cancers, I was aware that there was an increased risk of malignancy than the interaction of T cells and skin. And so I like doing these podcasts, I'm constantly learning. But is there a particular type of skin cancer? Does it include screens and basal cells,

**Dr. Chris Hillis** 45:22

typically, typically, basal cell and squamous as well, it's often the non melanoma skin cancers.

**Dr. Bill Evans** 45:30

Really interesting to know, what do you see in the future? You're doing clinical research at the Juravinski. And I know there's global efforts to keep improving the outcomes. The ultimate goal, I guess is can we ever cure CLL? It's a chronic disease, chronic diseases seem to be harder to cure than more aggressive diseases. So what do you see in the future? What are you working on at the Juravinski?

**Dr. Chris Hillis** 45:53

Yeah, so we have one curative therapy for CLL. And that's allogeneic stem cell transplant. And so that's where we take somebody else's immune system, and we put it in the person with CLL, to fight off the CLL and make sure that it doesn't come back. That therapy is, you know, highly effective for some diseases not as effective for CLL as some of the other diseases we use allo transplant for, but comes with a lot of long term health consequences. You know, allo stem cell transplant is not something that that is entered into without great thought. So our research goal would be to never have to do that, like we would like to create probably a functional cure more than a true cure for CLL. With what we know about the biology of CLL. Right now, there are patients like the the mutated patients that we talked about the more grown up lymphocytes that become cancerous, where we can functionally cure them with chemotherapy, and then subsequent treatments. You know, if people were to live to 150 years old, maybe not, but but with average life expectancy, our hope is that we can, you know, extend life with CLL, to meet that or nearly meet that, if possible. And so what what research we're doing right now, in clinical trials that we will be opening in the coming years, will be to move away from continuous therapy, we would like to further refine time limited therapy. So the BTK inhibitors changed everything for CLL. For the better for patients with deletion 17 P, for instance, which is a very high risk mutation to have, it offered an opportunity to actually get the disease under control and keep it under control for a good number of years, which we weren't really able to do with chemotherapy prior. But those are treatments that you need to be on continuously. And when you're on a treatment continuously, you're exposed to the risks of that treatment continuously. Again, we can manage the toxicities pretty well of these therapies. But it's much better to be off than on and so we're looking and we're doing some research studies at better combinations of medications, so that we can even take people with higher risk disease and put them on time limited therapy and not continuous. I'm hopeful as well, that we will be able to enroll patients on clinical trials looking at other treatments other than stem cell transplant, when they've been through a number of treatments. So if you live with CLL, for 1520 years, you're going to be on three, four different types of treatments in that time period. We've even seen studies come out where patients have had 11 lines of therapy, they've been on a lot, I can't name 11 different things. So I'm not sure what was what was their journey, but probably some repetition of treatments over the course of their CLL journey. So for those patients who have been on multiple different treatments, and maybe couldn't get a stem cell transplant because of age, or maybe we want to try something before we go down that road, I hope in the next year or two, we'll have access to some some novel treatments for that. Something we're quite proud of the Juravinski, which many of the listeners will know about as our car T cell program. And we may in fact be able to do a study of car T for CLL. To be honest, the results have been a bit mixed in that population compared to some other diseases that we treat with car T. But I think it is a reasonable thing to study for patients who've been through multiple different treatments, because it really does get at the CLL in a very different way than the drugs do. And that's often how we think about cancer therapy is the last thing didn't work. Let's not do it again. Let's try and do things in a completely different way. And so using car teas as an example would be a completely different way of treating CLL.

**Dr. Bill Evans** 49:34

So there's a lot of different strategies all aimed at one increasing survival but also the quality of life by trying to determine what's going to be the best for the least in certain sense, right? Least amount of time and least amount of side effects, the most amount of good quality of life off treatment. So

**Dr. Chris Hillis** 49:53

I mean the quality of life business for sure. First and foremost,

**Dr. Bill Evans** 49:57

was a good disease to focus on quality of life. One aspect of quality of life we sort of briefly touched on but maybe worth a few more comments is the psychological effects of having as chronic illness for a long, long period of time. Just the diagnosis of cancer, or leukemia sort of puts a weight on a lot of people shoulders very heavily. And, and the thought that at some point, it's going to need treatment or the treatments not going to work. And so what do you see in your practice in terms of the mental health of patients? And is it necessary to intervene at times or other supports for these patients are the groups of CLL patients together and support each other, for example, in the community,

**Dr. Chris Hillis** 50:42

we have a fabulous CLL Patient Network in Canada in Ontario, and certainly the support that's provided by peers, I think, can't be beat by any health care professional. No, I'm not living their life walking in their shoes, and so don't have the lived experience to be able to provide no advice in that sort of way that appear can share an experience with so So certainly, I think that is a very, very valuable resource to our CLL patients. Because when you're living with a condition like CLL, your experience through your cancer journey is going to be very different than say somebody with breast cancer or lung cancer or colon cancer. And so going to a generic Cancer Resource may not give you the kind of things that you might be looking for. Because your cancer is being treated with observation. And the resilience of these individuals is always astounding to me. But people do go through times where why am I not doing anything about this? Like I just keep going to the doctors, the numbers keep going up? And why will he not do something about this? And so people seek out information, are there foods I can eat as their exercise I can do we don't have any data to know what those sorts of interventions can do other than you probably should eat well, and exercise a lot. Like that's good for any type of cancer that people can have. So, you know, I think that reaching out to the CLL groups and peer support networks is very, very valuable for our patients because they can share and normalize those feelings of why are we doing nothing? Is this the right thing to do? And then other folks just show up and they say I only think about it for five minutes before I come to see and then I get on with my life after I see is so huge breadth of experience, I think and living with CLL.

**Dr. Bill Evans** 52:22

Well, that's really interesting to hear. And it's so terrific that we've got those kinds of supports of for patients and that they support themselves in these groups and in many different ways. We've covered a lot of ground here at Chris, it's been fabulous having this conversation with you. I hope our listeners have been enjoying it. As much as I have enjoyed it. I'm certainly glad you decided on medicine instead of hot tub sales, you would have been good at it. I think you'd be good at selling anything, but you're an excellent communicator. And so I just as we close out this podcast to just remind our listeners that they can listen to previous podcast by visiting the cancer Assistance Programs website, which is cancer assist on one word.ca I think there's about 50 podcasts there that cover a lot of different cancer types support group various supportive measures for if you have a diagnosis of cancer. So take advantage of that resource. You may find something that's helpful amongst our prior podcasts. And I really want to thank you Dr. Hillis for your willingness to be so thorough and engaging and using such great descriptions that help us understand the immune system and how it goes awry in CLL. And, and give us the optimism of the treatment center. We have now and treatments that will come in the future. So thank you so much for your time. Yeah, thanks. It

**Dr. Chris Hillis** 53:41

was great talking this morning bill.

**Narrator** 53:47

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