LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Partnering in Care: Chronic Lymphocytic Leukemia'

Description:

In this episode, we're joined by Dr. Marc Hoffmann from The University of Kansas Cancer Center, to explore chronic lymphocytic leukemia (CLL)—what it is, how it's treated today, and where research is headed. Dr. Hoffmann shares insights on treatment goals, side effect management, and the importance of shared decision making. We also touch on emerging therapies—including CAR T-cell therapy and bispecifics—and end with a message of hope for those navigating life after a CLL diagnosis.

Transcript:

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

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

Elissa: Today, we will be speaking with Dr. Marc Hoffmann, Director of the Lymphoma Program in the Division of Hematologic Malignancies and Cellular Therapeutics at the University of Kansas Cancer Center. He is passionate about clinical development of novel therapies for the treatment of chronic lymphocytic leukemia and lymphoma. He serves as the principal investigator on multiple clinical trials, including several studies of first-in-human compounds.

Welcome, Dr. Hoffmann.

Marc Hoffmann, MD: Thank you for the very kind introduction.

Elissa: Well, we are so happy to have you here; and so our episode today is on chronic lymphocytic leukemia or CLL. Could you explain to our listeners what that is?

Dr. Hoffmann: Yes, so CLL is the most common form of indolent B-cell non-Hodgkin lymphoma in leukemic phase. Okay, and so what does that all mean? So, indolent is a fancy word for slow growing. It literally means lazy. So, for anyone in the audience who's interested in 18th century British literature, indolent was an insult; and so you can read, Dickens where they're calling each other "indolents," and they're basically saying that that person's lazy. Well, it turns out if you have to have cancer, it's kind of nice to have it be lazy, right?

And so, it is an indolent disease, meaning that it just does not grow particularly quickly. Biologically, it's a B-cell non-Hodgkin lymphoma. It shares a lot more biological similarities with that set of diseases than any others. And then in leukemic phase basically means that it's zipping around in your blood. So, when we say lymphoma, we refer to cancer cells that are within the lymph nodes that are specifically blood cancer cells. And when we say leukemia, we're referring to blood cancer cells that are actually circulating around in the blood itself.

Elissa: Okay, so you mentioned lymphoma; and we often hear that CLL and SLL, or small lymphocytic lymphoma, are tied together as CLL/SLL. Is that why that is?

Dr. Hoffmann: Yeah, this is a classic example of academic debate, not necessarily leading to useful results for many years. So, the leukemia doctors found a disease they called CLL, and the lymphoma doctors found a disease they called SLL or small lymphocytic lymphoma. And everyone recognized that it was kind of the same thing. Most modern therapies, there's occasionally some differential activity in one compartment or another, meaning that there's certain drugs that may be more active in a lymph node compartment and others that may be more active in a blood compartment. However, by and large, the drugs are interchangeable; and we group the disease the same way.

And so, I don't know how many years ago it was, but it's within the last 10, 15 years or so, that they've actually unified the consensus criteria. So, CLL/SLL is considered to

be one disease. We use the same response criteria, the same basic parameters that we use to enroll patients on clinical trials are all used together. And soto be perfectly honest, it's a really nice development because it eliminates any trial bias where patients may not be eligible for a certain study based upon having a more lymphoma- or SLL-predominant presentation versus patients that have a more CLL-predominant presentation. We group them all together, and by and large, how well they do is dictated more by the individual biological aspects of their disease than necessarily the compartment in which it's occupying.

Elissa: Okay, and so how does CLL/SLL differ from other types of leukemias or lymphomas?

Dr. Hoffmann: So, biologically it's different. Right, so in terms of why does the cancer grow, and it turns out that there's a number of different ways in which cancers grow; and I would say that's probably the biggest piece is that it's really chronic B-cell receptor signaling that appears to drive a lot of the growth of these cells. And then there are certain subsets of CLL where there are unified pathways in terms of how cells die that may get disrupted. And for listeners that are familiar with some of the more biological aspects of the disease, when we say somebody has a 17p deletion or a p53 mutation, which is, certainly the most problematic and aggressive subset of CLL, what that's disrupting is the cellular machinery that engages in something called apoptosis.

So, apoptosis is programmed cell death and one of the primary ways it's initiated is through p53. And so, if p53 does not function, either because the chromosome which it's on, which is the p or petite arm, the small arm of chromosome 17 or the gene is somehow mutated such that it does not work, the protein is nonfunctional, you get the same result, which is basically that the CLL cells are much harder to kill. It's harder for them to die. They cannot initiate the death process on their own.

So, that part of it is something, quite honestly, which most solid organ cancers – so when I say a solid organ, I mean like breast, lung, colon, prostate, those types of

common cancers – p53 is nearly universally not functional in most of those cancers. And in blood cancers, one of the reasons why patients typically do a little bit better with blood cancers compared to others is that often that p53 is intact. So, that's a little bit biologically.

And then in terms of other leukemias, a lot of people will say, "Oh, my mother or my grandmother had leukemia; and she was really, really sick and in the hospital when she presented." And those are acute leukemias which are a very different can of worms. So, those patients, nearly universally, present sick, meaning they came to the doctor complaining of a problem. They said, "I do not feel well," and we get labs, and the labs show some major aberration in terms of their blood counts; and they're either sent directly to the hospital or sent directly over to a hematologist in order to get evaluated.

The most common presentation, by far, of CLL is an asymptomatic patient that went in for bloodwork with their primary care physician and their white count was noted to be mildly elevated; and they get referred over for evaluation. So, they're generally not sick at presentation. The vast majority of patients I see, it's highly uncommon. There's just a handful of folks a year who I see, and the very first time that I'm seeing them, unless they've been diagnosed elsewhere and they're getting referred in for a second opinion, but someone where I'm making the diagnosis, it's incredibly uncommon that I'm making a diagnosis and then immediately treating that patient with CLL. Whereas with acute leukemias you're pretty much having to start treatment urgently.

Elissa: Right.

Dr. Hoffmann: The treatments usually started within hours to days of somebody arriving in the hospital.

Holly: So, before we get into current treatments, let's visit what the goal of CLL treatment is. Is it more curable or is the goal more of disease and symptom management for quality of life?

Dr. Hoffmann: Well, I guess it depends on the individual patient, right? So, I think that the concept of curing the disease is definitively something that a lot of us in the field are interested in, right? So, I share this bias with a large number of other researchers in this field, which is that I'm attracted to highly effective, time-limited combination strategies to get rid of the CLL and then offer the patient the time where they're off treatment. And it looks like some of those combinations may actually result in what we call a durable long-term remission, which is their way of saying that it looks like it's probably not going to come back; but we can't quite say that the patient is cured.

So, that's sort of one way to answer that question. I suppose the easiest way, and this I say to patients almost always the first time I meet them, and I'm like, "Well, my goal is that you die of something else," right? Which is a very blunt way of thinking about it; but also, most patients are thinking about it. Most patients that are diagnosed with cancer, the question that they're asking themselves, they may not ask you that question, but they're definitely asking themselves, is, "Am I going to die of this?" "Is this life-threatening?" And for the vast majority of patients with CLL, it's not. Right, most patients die of other causes. And the CLL, a fair number of them don't even ever require therapy. They don't even necessarily need to get treated for their CLL.

So, in those patients, the goal is, "Well, let's look at what your treatment options are; and are you going to feel better or feel worse if I treat you? And if you're not going to feel better if I treat you and it's not clear based upon your lab values or your exam or other factors going into your disease that you're going to live any longer, then we really shouldn't be doing anything." I mean, medicine gets complicated; and I was just talking about genes and chromosomes. But I mean at the end of the day, you go to

the doctor because you either want to live longer or feel better. And if I'm not doing one of those things with treatment, then we really shouldn't be treating you.

And so, the goals are highly individual and also depend greatly upon the situation that a patient may be in. So, I'm 47I work full time. I have a family. My expectations are extremely high of myself to be able to go out and play golf and do athletic events and travel. And so, the way that I would think about the way that I wanted my CLL treatment is probably different than an 83-year-old who just had a hip fracture and is recovering from that and doing physical therapy, with a walker who may be a little bit more isolated. Right? Her goals may be different than mine, and they should be. That's natural.

And so one of the cool parts about treating the disease, you actually get to be a doctor. You're not just following an algorithm. You're actually talking to somebody and figuring out what's going on, understanding them, understanding what other problems they have in their life – both medically and, personally and sort of what's going on in their life sphere. And then, you get to figure out and make a decision about what they should do. And I would argue to you, particularly in this disease, if you're not doing that, then most patients are not getting the type of service that they need.

Elissa: Right, yeah. It sounds very like individualized treatment for that particular patient for that disease, which is great.

Dr. Hoffmann: Yeah, and that's 100% what it is. I was fortunate to be a part of a group that a guy named Jake Soumerai, who's up at MGH (Massachusetts General Hospital) in Boston, him and Debbie Stephens at UNC (University of North Carolina) organized, and I think there may be 15 or 20 of us; and it was looking at consensus recommendations about treatment. And when we sat down, we agreed about a very large number of things, which was awesome. But the one thing we agreed upon, which I can't say I'm surprised about, but I think was just a really cool statement of

where we're at as a medical community is there was universal agreement that patient preference is the number one consideration when selecting therapy in disease, right? What does the patient want? And your job is to help educate the patient to the extent that you can about what his or her options are, and then allow them to figure out what they want and to choose. And, sometimes patients don't want to choose; and that's okay. And then sometimes they want me to choose for them, which is okay. Sometimes, I have a recommendation or it's pretty clear what makes the most sense to do.

But their preferences and what's going on in their life makes a huge difference in terms of what they should do. And it can be, I'd say one of the big things that you have to do is make sure that you're turning off your brain in terms of what you think you might want because what I want is not, I mean that's not particularly relevant. What I want does not make a difference in that patient's life.

Elissa: Right. So, first, we actually did a patient video with Dr. Soumerai just last year.

Dr. Hoffmann: Wonderful.

Elissa: And so, we know him very well. And, second, it sounds like what you talked about with shared decision-making, which we talk about quite a lot on this podcast and really encourage our patients to do is to take an active role in figuring out what treatment is best for them.

Dr. Hoffmann: Yeah, and I think it's huge. To be perfectly honest with you, I think CLL is probably the easiest disease to do that with. I treat a broad spectrum of different lymphomas; and there's a lot of them where, Elissa or Holly, if you guys walked in my office, I'm like, "You need to do this."

Elissa: Yeah.

Dr. Hoffmann: And I might have a clinical trial or something else that sort of piggybacks along with the standard of care. But what you should or shouldn't do in a given scenario is pretty clear. Whereas, in CLL, it's just not. Right, there's not a huge body of randomized data to suggest which among our myriad of amazing treatments that we have available that have been developed in the last 10, 12 years is better than the other one. We know that all of those treatments are better than giving chemo. But beyond that you're sort of trying to figure it out; and, we sit in advisory boards and everybody, has their various opinions and agrees and disagrees about what they think, but at the end of the day, there's just not a lot of data that can help you sort through this.

And some of it's coming. It should get published. There's some bigger studies that are about to get published that we're anticipating those results; but I think even after those results get published, I'm not convinced that there's going to be one standard of care. I think there's going to be many, and I think it's still going to be a matter of thinking through risks and benefits and, how bad is your disease? Do you have low-risk disease? Do you have moderate-risk disease? Do you have high-risk disease? What are the characteristics? What do we know about how various therapies work with these various risk profiles?

And then, what other medical comorbidities do you have if any? And what are the toxicities and side effects of these treatments that you either want to be 100% sure you want to avoid or that you really don't want at all. For instance, somebody that lives four hours away from me in rural Kansas and does not live near anywhere that they can get an infusion, me making a recommendation that they get therapy that's infusional when they could do something that's oral is probably not the right choice, unless there's some very compelling reason why that should be the case.

Elissa: Right. So, let's talk about current treatments. You already talked about that some patients might not need to get on medication right away, so they'd be on watch

and wait or active monitoring, which we do want to be clear is still a treatment. But what are other treatments?

Dr. Hoffmann: Yeah. Well, I love that you brought that up because they had watch and wait, and then somebody turned it into watch and worry. And so, we had to change it into active surveillance, which you feel like you're doing something with active surveillance; and so, it's somehow more compelling. But it 100% is therapy. Patients with CLL who are untreated, have immune deficiencies that predispose them to infections and other types of cancers, and they certainly have some psychological impact from the disease, as well.

Now, this is highly variable, depending upon the patient. Some patients are affected more than others, as one would expect. But you're providing a fair amount of treatment in that context; and sometimes patients actually need specific therapy. So, there's those pieces of the puzzle.

The other part is the fact that they have CLL, if they are diagnosed with either a particularly severe or problematic infection or, more commonly, another cancer, the type of treatment that's recommended for that cancer has an impact on the CLL. So, for instance, as prostate cancer is commonly treated with radiation therapy, and they will often do imaging and find lymph nodes that are slightly enlarged in someone's pelvis, and then those lymph nodes get treated with the radiation field. And it's often assumed that those might be related to the prostate cancer. Well, if you do that, you're radiating the entire pelvis of that patient; and you have a lot of bone marrow in your pelvis. And so, I don't like my CLL patients not having as much bone marrow as they had before.

Elissa: Right.

Dr. Hoffmann: And so usually I have a very detailed discussion with the radiation oncologist, and I make sure that the plan makes sense, that we're not treating nodal areas of disease that don't need to get treated.

The messaging here, by the way, is not to not get radiation. It's just that if you do have a cancer that requires radiation therapy and you also have CLL, there should be a discussion between the CLL doctor and the radiation oncologist to sort of sort through what makes sense and make sure you try and avoid radiation to large marrow-containing areas as much as possible.

So, by and large, there's basically three classes of treatments that are commonly prescribed for CLL; and this is in the first line, second line, and then beyond second line is sort of a little bit more Wild West, where there's a variety of different things that are getting investigated.

Elissa: Okay.

Dr. Hoffmann: But the vast majority of patients will receive one of three types of drugs in their initial treatment of CLL, either something called a BTK inhibitor, which stands for Bruton tyrosine kinase. That's part of the B-cell receptor signaling apparatus, and that particular inhibitor – these are oral drugs; all of them are pills and there's three of them that are approved. There's ibrutinib, acalabrutinib, and zanubrutinib. They work extremely well.

These are your classic disease-modulatory agents. Right, so the intention of treating a patient with a BTK inhibitor is amelioration of disease-related symptoms, which it does a wonderful job of. So, people that have very big lymph nodes – sometimes I have folks that have lymph nodes that are the size of an orange coming out of their neck – those lymph nodes are often resolved within a week, two weeks, three weeks of being on treatment. It will eliminate night sweats, weight loss, what we call constitutional symptoms related to disease. If somebody has an enlarged spleen, it will help shrink their spleen. If their platelet count is too low or they're anemic, it helps to correct that. But it doesn't actually go out and kill the individual CLL cells.

Elissa: Oh.

Dr. Hoffmann: Okay, so that's in stark contrast to the other two classes, one of which is immune therapies; and these have actually been around for quite some time. It's an anti-CD20 monoclonal antibody, and the two that are generally used are either rituximab or obinutuzumab. In CLL, obinutuzumab is definitively more effective. There is actually randomized data showing that there's a survival benefit to giving obinutuzumab versus giving rituximab in frontline treatment of CLL. So, of the two, it's definitively the more effective.

It also has some increased toxicities. It depletes B cells at a more effective rate, and so it can lead to an increased risk of infections and other types of complications, infusion-related reactions compared to rituximab. Generally, those are things that are workable. They are our problems that you can plan for and account for and solve, but those drugs are actually going in and physically killing the CLL cells. And so those anti-CD20 monoclonal antibodies can be given either in conjunction with a BTK inhibitor, which we had discussed, or with something called a BCL2 inhibitor.

So, I talked a little bit about apoptosis before, what's called programmed cell death. One of the hallmarks of all cancers is the ability to evade apoptosis because a cancerous cell should die. Under normal circumstances, it would die if it didn't have derangements in apoptosis. It turns out that a BCL2 inhibitor, the way that those particular drugs work is that they allow the CLL cell to restore its apoptotic function and die off. And they also go out and actively kill CLL cells.

So, those are the three classes of drugs; and currently you can give all three of them together, you can give two of the pills together, you can give a pill and an IV, you can give a pill by itself. There's a lot of different ways, depending upon each individual patient and what their goals might be.

Elissa: Okay, so what about other treatments that we've heard about? Of course, stem cell transplant, CAR T-cell therapy, bispecifics?

Dr. Hoffmann: Yeah, so there's a lot going on. That's the Wild West. So, what we call double class refractory patients are patients that no longer have an adequate response to a BTK inhibitor and no longer have an adequate response to a BCL2 inhibitor. And it should be noted, just for the audience in general, that is a distinct minority of patients with CLL.

Elissa: Okay.

Dr. Hoffmann: Okay. This is a small number of people that actually fit this high-risk criteria. However, those are the people that keep us up at night. Those are the people who I'm actually worried about what's going to happen with their CLL. These are people that I'm not just seeing every three to six months and, we make sure they're doing okay, and then I'm spending the next 15 minutes talking about their golf game or their grandkids or whatever else we do in the visit that has nothing to do with their CLL whatsoever; but it's just us reconnecting as individuals.

So, there's been a number of different treatments that have been developed for them. And so, what CAR T cells are, are, and I'm sure that you have other podcasts on this, so I'm not going to go into huge amounts of detail. But essentially, the T cells are physically removed from the patient, at least in terms of all of the currently approved products. And they are genetically modified to kill B cells. Right, B as in boy cells; and, CLL cells are B cells. They are then infused back into the patient, and among the patients who respond, so patients that have something called a CR, or complete response, they do great. Right, they have an amazing time. Those who don't respond generally don't do very well, to be perfectly honest with you. We're looking at CAR T cells given in conjunction with BTK inhibitors, and so there's some other ways in which the CAR T can get modified to try and make sure that the T cell works a little bit better.

Bispecifics have a similar logic, right, which is that you're trying to get activated T cells to kill CLL; but they do it in a slightly different way. So, rather than physically

removing the T cells, we give the drug; and the drug is, when they say bispecific antibody, there's basically two ends. And so, it engages with the B cell itself, and then it also engages with the patient's, what are called endogenous T cells. These are T cells that are floating around in the periphery or sometimes in the lymph nodes, and then it activates those T cells to help kill off the CLL cells.

And most of the data in CLL that's been developed so far has been with a drug called epcoritamab. I've given it to several patients with CLL and with something called Richter's transformation, which is really awful CLL, to put it easily. But in the patients that respond well, they do extremely well.

And then there's also what we call noncovalent BTK inhibitors which sort of bind, and they can modulate, and overcome some of the resistance that we have to the covalent BTK inhibitors. And there is a drug now called pirtobrutinib that, that fits into that landmark. And then there's novel drugs being developed called BTK degraders that there's not yet an FDA-approved product in that class. But we're actively doing research on those drugs, both as single agents, meaning by themselves but also in combination, sometimes with bispecifics, sometimes with BCL2 inhibitors; and then there's new BCL2 inhibitors getting developed, so there's all sorts of stuff that's out there that's getting developed or that is actually currently available to give to patients.

Elissa: Okay, is there a particular target that you're going for on the B cell that would distinguish it from healthy B cells?

Dr. Hoffmann: I wish. That's actually part of the problem in terms of the toxicity profile of the drug. So, it turns out you can live without B cells. So, you can live without B as in boy cells; and so, when I said that BTK inhibitor and I said it was a Bruton tyrosine kinase. So, there was a guy named Dr. Bruton who identified a disease that was a congenital absence of gamma globulins. Basically, these patients did not produce antibodies; and so, it was kids that presented early in childhood with

recurrent infections. But they didn't die, okay. Now, not having T cells is not an acceptable situation.

Elissa: Right.

Dr. Hoffmann: So, one of the reasons we've had trouble developing CAR T cells for T-cell lymphomas is that we end up killing all the innocent bystanders. And the sine qua non of that is HIV and AIDS, right, where that disease, it just eradicates and it only eradicates one part of their T cells. It doesn't get rid of all of them, but just not having the CD4-positive T-helper cells results in patients dying. But you can live without B cells.

So, we use targets that are common on B cells; and so, the currently available bispecifics, the epcoritamab is an anti-CD20, so it uses the same target as rituximab and obinutuzumab. And then the CAR T cell that's available, which is called liso-cel, targets CD19. And CD19 hits earlier, it's more of like what we call a pan-B-cell antigen, meaning it's present on a lot of B-cell cancers. And so, you can use a CD19-directed CAR to treat a whole menu of different diseases, whereas a CD20-directed CAR has to have CD20 expression, and there's a little bit more limited set of options there.

Unfortunately, in all of these situations, we are not only eradicating large numbers of healthy B cells and in many cases, you're actually trying to make the patient B-cell aplastic. But also, the T cells are getting redirected, so inCAR T-cell therapy, you have the CAR that's out there, that's the T cells and what's called the lympho-depleting chemotherapy that we give, takes the patient's own T cells, and they don't work as well as they used to, and so they end up getting some weird infections afterwards.

And similarly with bispecifics. Those T cells that you're redirecting at the cancer are less inclined to do their own job, and they end up neglecting coverage of latent viruses and a variety of other, we call opportunistic infections which are types of infections that don't affect healthy people but do affect people that are immunocompromised.

So, that's part of the risk that's associated with those therapies. Even though they're B-cell depleting, they also cause challenges with T-cell functions, so you end up with problems in both domains.

Elissa: Right, so what about stem cell transplant? Is that a possibility, particularly, with younger patients?

Dr. Hoffmann: Yeah, it is. So, what's called an allogeneic stem cell transplant, meaning that you're taking somebody else's bone marrow and transplanting that in, I will still frequently refer patients for that procedure if they are young and fit and healthy, and if they are what we call double-class refractory, meaning they are no longer responding to a BTK inhibitor or a BCL2 inhibitor.

There was a lot of debate still, and I don't necessarily know that we have the correct answer about whether patients should 100% receive CAR T-cell therapy before going to transplant or not. Some of the challenge of that is that the data sets that are looking at both of those modalities, it's a little hard to compare the two. But it's about 20% of patients that get CAR T cells that really do well, that go into a complete remission and have durable long-term success. And the other 80% they have a lot of the side effects from the CAR T cells, and they may be a little less fit to go into transplant. And so, we have this debate a fair amount.

Transplant, the cure fraction is a little bit higher. It seems probably about 40%. It kind of depends upon what series you look at. But the amount of CLL that you have going into transplant has a big impact on the disease.

The problem with transplant is that there's also a significant number of patients who, unfortunately, die of transplant-related complications and are in remission from their cancer. So, it is an option. I do use it. There's very unique and highly unusual situations in which we pretty much always do it. Somebody has brain or spinal fluid involvement with CLL, which again is extremely rare. But when it happens, we take all those patients to transplant and I have a handful of folks that have done that. And

then patients that may be relapsing but not floridly or we've figured out a way to get their disease under control; and they're largely in remission. A lot of those patients will shunt to doing an allotransplant because I'm a lot less worried about them having early progression in the transplant period. So, it's a complicated set of decisions, and there's not clearly correct answers. And I would say if you asked a number of folks internationally in the field, you're going to get a lot of different answers about how they think through these patients.

And it gets down to individualization again. This is sort of the most radical way that you're individualizing therapy, right, choosing between two options that, quite frankly, nobody wants. Offering people pills is a slightly different concept, but offering transplant and CAR T cells, it comes with nonnegligible risks of those therapies actually, unfortunately, killing the patient. But you're doing that, obviously, to get a durable, long-term remission. So, those are our nuanced conversations, and I would say that there's not a clear consensus surrounding how to do that.

Holly: Okay, so we just discussed a lot of current treatments for CLL; and, obviously, with treatments comes or poses the risk of potential side effects. What are some side effects patients may have from treatment, and are the side effects manageable?

Dr. Hoffmann: Yeah, and I guess the first one that comes to mind is financial, right? All these drugs are really expensive, and so especially pills. It turns out that the IV portions of therapy, if you actually go to an infusion center, that comes out of the hospital portion of your benefits, whereas if I write you a prescription for a pill, that comes out of your pharmacy benefit. And those are two different buckets of money and may not be managed by the same group of people and typically are not. We don't need to get into all those details, but all these drugs are really expensive.

So, the first one is making sure that your insurance coverage is up to date and active and that you have, appropriate plans in place, particularly people that are newly diagnosed with CLL, maybe you're going onto a Medicare plan or something like that.

You do not want to be on a cut-rate Medicare Advantage plan with CLL because your drugs are not going to get adequately covered, you're not going to be able to enroll easily on clinical trials. The Advantage plans are not always accepted at a variety of different institutions, and so it can limit the number of places that you can go. And so, I'm not saying all Advantage plans are bad, but you're going to get what you pay for. And if it's a whole lot cheaper to be on the Advantage plan, there's something that they're not giving you because healthcare's expensive.

So, that's just sort of a financial toxicity review. If possible, I usually tell people just do straight Medicare with a supplement. But sometimes that's not financially viable. So, figuring out ways to negotiate that is important. It's a common thing that we have our financial coordinators get involved with patients to help them sort that out.

In terms of the actual medical toxicity, so the BTK inhibitors, again, that's ibrutinib, acalabrutinib, and zanubrutinib all essentially have similar class effects; and then there's a couple of nuanced differences between them. So, all of them can cause some bruising and bleeding, and so patients will often bruise a little bit more, particularly if they're on aspirin or some other type of blood thinning agent. They all can cause diarrhea; and, most of the time it's not really severe or dose-limiting, but occasionally patients just don't react well to one particular drug. And then you often switch them to something else, and typically you can find one of those three drugs that's workable for them.

They can get a rash, and typically a rash is not common. It's not mild. It's usually pretty much all over your body. Like you're not wondering whether you have a rash or not. You walk in, and you're like, "I have this rash, and you need to get rid of it for me." That's typically not necessarily specific to one drug or the other, so somebody has a rash for one drug, that does not mean they will have a rash with some of the other drugs.

And then there's some unique toxicities, so acalabrutinib can cause headaches, particularly in the first 30 days or so. Generally, they're not something that causes patients to have to come off therapy. And usually if you can wait out the period that you have the headaches, they do go away. And then ibrutinib and zanubrutinib are both associated with hypertension, which acalabrutinib by and large does not.

And then I'd say the biggest risk factors associated with them are cardiac risk factors, which are mainly heart arrhythmias. So, atrial fibrillation is the most common; and ibrutinib causes more AFib (atrial fibrillation) than either acalabrutinib or zanubrutinib. But it can be problematic.

Now, patients that are already in AFib, so there are some patients that come in and they have chronic atrial fibrillation; and they've been in atrial fibrillation for the last five years, generally it doesn't make it worse, right? So, it's more that it actually causes the rhythm problem; and then there are some reports of more problematic rhythms. So, atrial fibrillation is an atrial arrythmia, meaning that it's not in the ventricle which pumps blood throughout the body. Ventricular rhythms, in general, can be fatal. And there are certainly reports of BTK inhibitors being associated with ventricular arrhythmias, and so if somebody has very severe structural heart disease, they've had multiple large heart attacks, they are predisposed to getting ventricular arrhythmias, that can often make me a little bit skittish about giving them a BTK inhibitor.

In terms of the other drugs, so the anti-CD20 monoclonals, obinutuzumab and rituximab, it's predominantly B-cell deficiencies and infections; and then there's an annoying side effect of an infusion reaction, which is that while the drug is actually getting infused, the patient's immune system gets ramped up and they essentially get what looks like some serum sickness. So, you can get some shaking, chills, fevers. Most of the time it's just annoying. We treat it, we turn the rate down and then restart the infusion. And so, it's generally more of an annoyance than it is anything else. But it certainly can happen, and I would say particularly for obinutuzumab the first day, I usually tell patients you're going to have a reaction of some sort. Even if it's just a

scratchy throat or you run a short fever. Something's going to happen on that first day; and, typically, the second day, it either doesn't happen or it's a lot less severe.

And then the BCL2 inhibitors, and the one that's currently FDA approved is venetoclax, it can cause some lowering of the blood counts which generally is not symptomatic, meaning patients don't say, "Hey, my neutrophil count is low or my platelet count is down." They don't feel bad from it, but it is something that we notice numerically; and it can be associated with some infections, particularly if the neutrophil count is low on a prolonged basis. You can treat through it, so I generally don't stop the drug. I just give growth factors, which are drugs that we use that are shots that sort of stimulate the bone marrow to make extra neutrophils; and most of the time you don't have to interrupt therapy to just treat the low counts.

The other one is something called tumor lysis [syndrome], which basically is that the drug works so well that the CLL cells break open and release their salts into the blood; and it turns out that in the process of releasing the salts, salts that are within our cells are different than the salts that are within the blood and serum and other fluids, and they can cause problems, predominantly heart rhythm issues and kidney dysfunction.

In general, with venetoclax given the way that we give it now, which is an escalating schedule, those patients sort of ramp up over the course of four to five weeks, we don't really see much tumor lysis at all. So it's a very uncommon complication; but it is something that's annoying. You have to get labs every week that you're coming in to increase your dose. You have to take some extra drugs in order to prevent it from causing problems and increase your fluid intake. And so, it's an inconvenience to have to give the drug just, from a practical standpoint that the patients have to come in and get blood for monitoring.

But once they're up and running on it, generally the venetoclax is pretty straightforward. Occasionally, a patient will have some loose stools, but generally not

horrific diarrhea or other things that are dose-limiting. So, once you've gotten it started, it's generally not that big of a deal.

Holly: Okay, let's discuss the future of CLL treatment. Are there any emerging therapies or those in clinical trials that you're particularly excited about?

Dr. Hoffmann: Yeah. As I said at the beginning, I personally have a bias towards time-limited, meaning that you're giving therapy for a specific time period; highly effective, meaning that it's leading to a very deep remission and you're killing lots of CLL cells; therapies that then lead people to not be on treatment for some period of time. A fair number of patients don't really want to have to take a pill every day if they don't have to. Some patients don't care, right? But a lot of patients don't.

So, there was a study recently presented called AMPLIFY which looked at a conventional chemoimmunotherapy platform and compared that to two different styles of time-limited treatment with either acalabrutinib and venetoclax, which was all oral, given for a little over a year, to a triplet therapy, which was acalabrutinib, venetoclax, and obinutuzumab, which was also given for the same duration. It was 14 months, so a little over a year.

So, that's really starting this trend towards, hey, do we have all oral treatments that we can give people for a defined period of time? That study was not compared to some of the other highly effective therapies. So, obinutuzumab and venetoclax is the other time-limited treatment that's about a year. That particular regimen was not directly compared to acalabrutinib and venetoclax, but that trial is ongoing. I think it's done recruiting, but it certainly hasn't been reported. That trial's called MAJIC, and there's another trial called CELESTIAL, which is looking at obinutuzumab and venetoclax, which is a doublet arm of two drugs versus zanubrutinib, a different BTK inhibitor with a different BCL2 inhibitor called sonrotoclax. And that combination of all orals, I think, is quite an exciting one.

So, in terms of frontline therapy, we now have options. One of the challenges in AMPLIFY was that the people that got three drugs, there was actually a higher risk of death, at least early on among the patients that had the three drugs; and a lot of it was infections. And, it was conducted during COVID; and a fair number of the patients were vaccinated, but unfortunately still succumbed to their disease.

And so, there's a question about the toxicity, and there's questions about how relevant is that in post-COVID era, where we don't see patients having nearly the number of certainly fatalities related to COVID that we saw back in the height of the pandemic. So, there's been a little bit of that, but definitively giving three drugs is more toxic than giving two, right? And so that sort of bore out in those data sets.

The other thing is that acalabrutinib and venetoclax, in terms of leading to really deep remissions, and this gets into something called MRD or minimal residual disease, the negativity rates, meaning the, the rates that we had undetectable MRD, were a little bit lower than what have been seen in some of the other doublets. And so, there's been a little bit of a question of do we either need to give it longer, MAJIC allowed for patients to receive that therapy for up to two years, depending upon their MRD status; or do the drugs and the backbone need to be different? Do we need a different BCL2 inhibitor or a different BTK inhibitor?

So, those are some of the questions that are being answered. I would argue too that those data sets are going to be more relevant to the vast majority of CLL patients than me talking about degraders and various other compounds that are in development. They're really cool, but they're really intended to overcome relative resistance to standard therapies.

And so, I think the biggest movement in the next five to ten years, I think there's going to be two of them. Well, I'm going to give you three. So, one is that I think we're going to end up having defined course regimens for the vast majority of different types of CLL. So, highly effective, time-limited treatments that lead to durable

remissions that should be available for most patients, both in the frontline and then potentially in the second line.

The second thing is I think we're going to have even more toys, in terms of overcoming some of the relative challenges of managing patients who no longer respond to BTK inhibitors and no longer respond to BCL2 inhibitors or have some unacceptable toxicity to both classes of drugs and can't take them. So, we'll have more toys in the toolbox.

And then I think the third thing is that I think there's going to be some way in which we use immune therapy, so whether that's a bispecific or whether that's a CAR. But, something in that domain is likely to be approved; and I expect that that therapy is what's going to help the most with what I'd mentioned before, which is something called Richter transformation, which we're seeing more of now, quite honestly, that CLL patients are living longer. Right, they're living longer, they're doing better with their CLL, and so, they actually have an opportunity to develop this transformation, which remains quite a challenging clinical problem.

So, I think those are the developments.

Elissa: So, our final question today, Dr. Hoffmann, on our patient podcast home page, we have a quote that says, "After diagnosis comes hope." What would you say to patients and their loved ones to give them hope after a diagnosis of CLL?

Dr. Hoffmann: Yeah, I mean, it's an odd position to be in because I have family members that have CLL, so I've sort of watched them go through the mental gymnastics of, the lab abnormality and thinking that that might mean something and then arriving at a diagnosis and then realizing that the diagnosis may not be that bad, right? And, then living for many years before needing treatment and then requiring therapy. So, I've seen this play out not just with patients but also in my own family.

And what I would say is that the initial diagnosis is always going to be a little bit shocking, right?

Elissa: Yeah.

Dr. Hoffmann: And so, one of the things I do is always try and paint things in a positive way. It depends on the patient situation and their makeup as well. I will never forget this. I have this patient who's, I can't remember what I was following her for. She had some other kind of lymphoma. I don't remember what it was, but her white count, it was always up. And I was like, "Oh, maybe I should go and look in and figure this out." And so, I sent off something called a peripheral blood flow cytometry, which is the common way in which CLL is diagnosed, and it was positive and it showed CLL.

And I didn't know what she was going to think. I was really nervous. I pulled her back in, and we talked about it for a little bit. And, she's 82 at this point, at the time that she was diagnosed. So, she's like, "So, I don't have to do anything about it?" And I said, "Yeah, I'm pretty sure you're not going to have to do anything." She's like, "Oh, great. All right, well when do you want to see me again?" Right, and so for her it was a non-issue. Right, so there's folks in that category, which I guess you could hope to be in that category, in which case you really don't care and you've got bigger fish to fry. But I think the intention of the quote was not that individual but the younger person, right, or somebody who recognizes that they have a lot of life in front of them they want to live.

And what I would say is that the biggest piece of having the diagnosis for most people is figuring out how to make friends with it. And what I mean by that is not that, somehow you love having CLL or that you can't wait to tell everybody that you have it, and you're happy about it or something along those lines. But more that you don't reject the idea that you have this new diagnosis and that you figure out a way to live with it and have it be a part of your existence. And at various points in your life, it's

not going to be that big of a deal, right? I'm sort of like their dentist. I see them a couple times a year, and, they get their checkup and you don't need a filling. All right, then I'll see you in six months.

But, then there's other times where we actually need to think about things that are a little bit more serious. And I think the other part is just having confidence that there's a large number of treatments out there that we'll be able to integrate with your lifestyle, whatever that is. So, if you're somebody that likes to live six months in one place and six months somewhere else – I have a lady that she came to me and said, "I'm going to travel around the world, and I'm going to be gone for 11 months, and we need to figure out how I can treat my CLL while I'm gone." And we figured that all out and she was able to get her therapy, and she took pills the whole time and she did awesome. Right, and so she's in Thailand. She's backpacking through Kenya; and so, this is something where it is a part of your life, but it does not have to control your life, right?

So, you can either own your CLL, or it can own you; and part of being friends with it is respecting its power. This is something that's powerful, and you need to respect it. And at the same time, not allowing that to have it own you and maintaining your own capacity to work with it.

And so, it's kind of the way that I think about it, and it's a discussion that I have with patients all the time.

Elissa: Yeah, thank you so much, Dr. Hoffmann, for joining us today and for this wonderful discussion all about CLL. And it was so exciting to hear about these new treatments and potential treatments on the way. And so, again, we really appreciate you being here with us today.

Dr. Hoffmann: Well, it was absolutely my pleasure Elissa, Holly, and, any patients out there, it continues to be our pleasure to serve you and so thank you guys for putting together these materials.

Elissa: Thank you.

Holly: Thank you.

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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