LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: '"CLL: Risk Factors, Resources and Research'

Description:

Join Alicia and Lizette from The Leukemia and Lymphoma Society as they speak with Dr. Ann LaCasce, Program Director of the Dana-Farber/ Partners CancerCare Fellowship, the largest hematology/oncology training program in the country. On this episode, Dr. LaCasce explains the difference between chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), CLL and its connection with Agent Orange exposure, resources available for Veterans, current and emerging therapies, clinical trials and the importance of medication adherence. Dr. LaCasce shares her excitement for what is to come for CLL treatment and her appreciation for fellow providers around the world, who work to move science forward as they continue to learn from each other.

Transcript:

Alicia: Welcome to The Bloodline with LLS. I am Alicia.

Lizette: And I am Lizette. Thanks so much for joining us on this episode.

Alicia: Today, we will be speaking with Dr. Ann LaCasce, who is a Program Director of the Dana-Farber/ Partners Cancer(Care) Center Fellowship, which is the largest hematology, oncology training program in the country. She is an Associate Professor of Medicine at Harvard Medical School and performs clinical research in lymphoma. In addition, she has a strong interest in young adults and co-directs the Center for Adolescent and Young Adult Oncology with Dr. Lindsay Frazier at Dana-Farber. We also spoke with Dr. LaCasce on another episode about CLL discussing diagnosis, treatment and other information so we encourage you to listen to that episode as well, which can be found on the episode page on thebloodline.org. Thank you so much for joining us, Dr. LaCasce.

Dr. LaCasce: Thank you for having me. It is a pleasure.

Alicia: So, we are going to jump right into a discussion of CLL and just to preface this conversation, what is CLL for the listener that is on today?

Dr. LaCasce: So, CLL is a cancer of the lymphocytes. So, B-lymphocytes are one of your immune cells. They arise out of what's called a bone marrow stem cell. Those are cells that live in the bone marrow and give rise to all your blood cells—white blood cells, red blood cells, and platelets. And CLL arises out of a subset of white blood cells, called the B-lymphocyte, whose normal job is to make antibodies that help you fight certain types of infections. You get a mistake in the machinery of that cell and that cell gets a signal to copy itself and you get a collection of abnormal cells that are growing, abnormally, basically.

Alicia: And what are the two different forms of CLL?

Dr. LaCasce: So, CLL, chronic lymphocytic leukemia, and small lymphocytic lymphoma, we sort of think about as the same disease process. They just sort of present in a slightly different way—in order to fit the category of CLL, you have to have more than 5,000 B-lymphocytes in the peripheral blood. So, if you have the same disease and you have fewer than 5,000, then we call it small lymphocytic lymphoma. Most patients present with lymph node enlargement. All patients essentially have disease within the bone marrow and it also can be seen in the spleen. So, it's really two forms. Most patients present with CLL. It is also a fluid definition, as patients live with the disease longer and the white count goes higher, a patient may sort of transition out of being called small lymphocytic lymphoma to being called CLL. There is also what's called monoclonal B-cell lymphocytosis, which is sort of a precursor to CLL. So, if you have no enlarged lymph nodes or spleen and the absolute number of B-lymphocytes in the blood is under 5,000, then that is actually a precursor

to CLL; and many of those patients will never need any therapy and are just followed, you know, once a year with blood counts.

Alicia: Reading up about CLL and looking to see the connections to certain groups I was reading that in 2002, the Department of Veterans Affairs added CLL to the list of diseases with sufficient evidence of an association with Agent Orange exposure. Has there been more conversations about that?

Dr. LaCasce: Yeah; I mean I think there--this is one of the things that we—is considered service-related. So, when we see veterans who have CLL, or all non-Hodgkin lymphoma and Hodgkin lymphoma are also considered, service-related because there is evidence that the herbicide that they used, the Agent Orange, apparently came in drums that had an orange stripe around them. That's why they called it Agent Orange and it was used to defoliate the jungles. It contains dioxin, which is a carcinogenic and there has been some link with that and CLL, but data is a little bit hard to tease out, but it is considered by the government to be related to Agent Orange.

Dr. LaCasce: And, you know, we also see patients who live in rural areas and there is clearly an association with farmers and mantle cell lymphoma, which is a slightly different, but related type of lymphoma. So, I do think that environmental toxins may play a role in CLL.

Alicia: And, like you said, it is probably so difficult to pinpoint because there is research, but then there is other research that may expound on something else. You are not entirely sure what to connect it to so I understand how it can be confusing for a physician and for a patient, as well.

Dr. LaCasce: Yeah; the data is very difficult when you look at associations because there may be things. So, for instance, if you have a group of veterans that served in Viet Nam, that's going to be men. CLL is more common in men. You know, maybe there are more of these individuals who are from rural areas or from, you know—so you really have to look and try to account for anything else that could be driving the association and it's very difficult to do that.

Lizette: My father was in Viet Nam and, as you know, the Veterans Administration does have resources for folks who are diagnosed with these types of cancers. So, Viet Nam veterans, if you are listening, as well as other veterans, anybody, that has been exposed to Agent Orange, you can give us a call and there is a special line for the Veterans Administration to get benefits and to make sure that you are treated.

Dr. LaCasce: Yeah; it is very important and, ah, I think it is a good resource and we owe that to our veterans who were in Viet Nam to, you know, to treat them well.

Lizette: And it is also on the list for the World Trade Center.

Dr. LaCasce: Yeah; you know, there isn't much scientific data that I can find with an association and the thing that is a little bit unusual, in my mind, is that, you know, this happened relatively recently and we think of environmental exposures as having a relatively long latency before the cancer develops. And there are a large number of diagnoses that are considered associated with the World Trade Center. So, and I know that they, also, are following people who were first responders very carefully. In fact, I have a patient, who was picked up as a first responder, who is having serial blood draws and looking for things; and he has CLL. And he is relatively young, so maybe there was an association, but typically, you think about, you know, a sort of more chronic exposure; maybe people who are working at this site over longer periods of

time. It is hard to know, but I think—I think it is great that it's considered covered and if there is any association, we need to help those folks.

Alicia: Absolutely.

Lizette: And you mentioned farmers and you know pesticides and herbicides, people in rural areas and those are folks many times, that don't live near any of the comprehensive cancer centers or may not have access to routine care. Is there anything that we can provide—some tips on what to do? People are always asking.

Dr. LaCasce: Yeah; you know I think, given the internet and just the way that medicine and medical centers are sort of evolving, there are now many places have close ties with rural areas. So, for instance, here where I work, we have very close ties to multiple places in Maine, New Hampshire, Vermont, so there are oncologists whom we know very, very well who send patients down when they need clinical trials or if the patient—sometimes it's just not feasible financially to come into Boston, but we can serve as consultants for those oncologists and know those people really well. And I think that that is true in many rural areas; that there are networks now of physicians at major cancer centers who have close ties. So, I think, you know, patients need to try to advocate for themselves, which can be very difficult. But I think just asking the questions and asking, you know, would it be worth my while to get a consult and, sometimes, there are resources available to help people do that. Alicia: And to your point, yes; technology serves as a wonderful resource. It can be a horrible resource at times, but-

Dr. LaCasce: Oh yeah.

Alicia: -but it definitely can have its perks. And when someone, you know, needs that information, we highly encourage them to call our information specialists and,

once someone calls, they can speak one-on-one with one of our information specialists who can assist them through cancer treatment, financial and social challenges, and give them up-to-date information about their disease because, like we said, online you see everything and to actually have that connection with individuals who have done the research for you and are masters' level oncology, social workers, nurses and health educator. We highly encourage people to call them and that number is 1-800-955-4572 and they are open Monday to Friday, 9 a.m. to 9 p.m. Eastern time. And we also encourage people to utilize a lot of our online resources. We know that it is hard to, like Lizette said, get to places so, by logging onto a chat or by joining our LLS community, people can connect with others who have either the same disease or maybe similar situations where they can ask questions and feel empowered to bring back to their healthcare teams. So, we definitely encourage people to also look at all of the support resources that we offer; and that website is www.lls.org/support.

Dr. LaCasce: Yeah; I think these are invaluable for patients. You know, when you meet with a new patient and have an hour, you know, somewhere between an hour or an hour and a half usually, initial consult, it is so completely overwhelming and we go through so much information that we leave patients completely, you know, overwhelmed with lots of questions aft—that come up after they leave. So, I think being able to sit back on their own time, after they've digested the information a little bit, and then hone in on questions and have the availability of these types of resources is really amazing.

Alicia: Absolutely. So, before we jump into clinical trials and new therapies, what are the existing drug therapies that are being used right now CLL patients?

Dr. LaCasce: So, when we approach therapy in patients with CLL, we look at a couple of different things. One is what is the age and fitness of the patient; if they are under 65 and in good shape, or are they older and more frail? And many of our

patients are older and more frail. And then we look at the characteristics of the disease. So, we look at what are the chromosomes, or the cytogenetics, show. Does the patient have a 17p deletion, or complex chromosomes, or a mutation in what we call TP53?

We also look at what's called the immunoglobulin heavy chain mutational status, but by looking at those factors, you can really select the right therapy for a patient, or the right couple of possible therapies that you want to discuss with the patient. So, for younger patients under 65 who are mutated, which is favorable, has a good prognosis and do not have 17p deletion, we typically use old school chemoimmunotherapies, so fludarabine, Cytoxan® and Rituxan® because the percentage of those patients may actually be cured of their disease. You know, you have to follow people for many years to really be able to say that, but there is data, both from the West and from Europe, that suggests a proportion of those patients are actually cured. So, that we would do for those younger patients.

For younger patients who are unmutated, so that's unfavorable, have 17p deletion or complex cytogenetics, then there are other options. 17p patients typically go on the novel oral drugs, like ibrutinib, because they do not respond well to standard chemoimmunotherapy. The disease tends to stay in remission very briefly so we use those therapies.

For people who are sort of in the middle, they are unmutated but do not have 17p, we discuss options including time-limited chemoimmunotherapy, either fludarabine, Cytoxan, and Rituxan. If they are young, then bendamustine + Rituxan, for a limited number of cycles, or we talk about the novel agents, which are very effective, but people need to be on for long periods of time. These agents can also be associated with side effects like abnormal heart rhythms like atrial fibrillation or bleeding.

For elderly patients, we typically look at Chlorambucil, which is old drug, alkylator drug in combination with a new drug, obinutuzumab, which is like Rituxan, but a little bit more potent and more active in CLL; and that is a very good option for an elderly patient. Or we think about ibrutinib or potentially one of the other novel oral drugs. So, it is not a one size fits all. You really need to look at a number of different characteristics of the patient. What their preference is and the characteristics of his or her disease.

Lizette: And many of these new drugs are also oral medications, right?

Dr. LaCasce: Yes; very exciting.

Lizette: It is very exciting and usually it is, you know, a lot more convenient for patients, but we do find—and since you do work with adolescent and young adults—that sometimes there is issues with actually taking medication at home.

Dr. LaCasce: Yes; it is a big issue. It can be, sometimes patients forget. These are very expensive medications. Fortunately for the majority of our patients, we live in the U.S., and fortunately most people can get these medications at a reasonable cost or, if the cost is high, we can usually find some assistance for many of these patients, so that's one barrier. And taking the medication every day, you know, the data shows that many patients are not taking the medications as prescribed. And the thing we worry about a little bit in that is that, you know, if you are not taking your medication, just be honest with your physician because what can sometimes happen is people can become resistant to that treatment. If you are taking it on and off, the tumor cells are not getting a continuous sufficient exposure to the drug and it can make it easier for those cells to outsmart that drug. So, we know that it is not easy so we need to work with patients and, you know, don't—I would say to patients, "don't be embarrassed or

feel like you can't admit that you missed a drug or you just don't like it, or whatever it is. We need to work with you and figure out an alternative strategy."

Lizette: And do you find some patients don't take medication because of side effects.

Dr. LaCasce: Oh, all the time. You know, with ibrutinib, which is a very active drug over time, a significant proportion of patients come off for side effects. We can reduce the dose. We now know that a lower dose, particularly in older patients, may be very effective so it is not like you have to take the full dose or none at all. You know, we try to work with people and figure out what can you tolerate because, you know, we are not doing anyone any good if we prescribe it and think you are taking it and you are not because you just feel crummy; let's figure something else out.

Lizette: Sure.

Alicia: We were talking to another doctor and she was saying that, like Lizette said earlier, because of the cost of the drug, that person will say to themselves, "I can stretch this drug out. I can take it every other day" or they might say, "oh, I am actually feeling good today so I will just take it when I start to feel, you know, badly" so I think oral adherence is something that it's--you're happy because it is oral, but then you are thinking, no, but you have to stay on it in order for it to actually do its job.

Dr. LaCasce: Right; I mean I think we were all really excited initially to have all these oral drugs, but over time, you realize there are definitely some advantages to coming into the clinic and getting your infusion and coming back a few weeks later. So, it's—they're just very different and I think that is something we talk to patients about particularly when there is an option for, you know, upfront chemoimmunotherapy or starting a new drug that you are going to take indefinitely by mouth every day. Some

patients know themselves and say, "no, I want the short-term in-and-out and then when it comes back, then we will figure out what to do next."

Alicia: When you are speaking to your patient and you are discussing therapies for them and the topic of clinical trials comes up, how does the patient usually receive that or what's the common reaction that you get?

Dr. LaCasce: It really varies. You know, a lot of our patients with CLL, because they're on active surveillance for a period of time, many of those patients are pretty savvy and have read online so they know what a clinical trial is. Occasionally, you will get patients who will say, "well, I don't want to be in the placebo arm". You know, you really have to take time to explain the ethics of doing trials and what the goals of doing trials are and what the risks and benefits are. So, it is quite varied. Some people come in specifically saying, "well, what do you have that is new and exciting that may not include any chemotherapy because that is what I want", but on the other hand, you may have people say, "well, if it is not approved by the FDA, I am not going to be a guinea pig". It takes time to really explain to people why, you know, what a trial is, what the goals are and why it may or may not benefit that individual patient depending on what phase it is. So it takes a lot of education and I think, you know, having programs like you have, you know, where you educate patients on exactly what trials are that these are very important.

Lizette: I am glad you are talking about the education because, we have gotten a lot of calls here and our information specialists are talking to CLL patients all the time who have called. They are on active surveillance and they are asking to go directly to a CAR T-cell trial.

Dr. LaCasce: We see that, you know, and—or, you know, if this is a disease that you are telling me is not going to be cured with standard treatment, why don't I get an

allogeneic transplant now. So, you really have to explain that these are life-threatening therapies that you may not be looking at, ever! You may never need them and, you know, you really have to balance the side effect profiling and use them when appropriate if the disease is not responding to better tolerated and standard therapies.

Alicia: We hear the same things, guinea pig, placebo, sugar pill, last resort. We hear all of these things and on one of our other episodes, we spoke about clinical trials and definitely just want to get the message out there that this is something that every single drug that people are now using came from a clinical trial. And clinical trials serve as research and preparation and it serves as something that can potentially help future generations even. So, I definitely appreciate the fact that, like Lizette said, you speak about education of these things.

Dr. LaCasce: And if you look at the drugs we are using now every day in the clinic, ibrutinib, venetoclax, obinutuzumab, these were drugs that were in clinical trials and are still in clinical trials, but, you know, even just a few years ago; and I think things have really changed in terms of the rapidity with which we get drugs to patients. I think the FDA is really—you know, you have to strike a balance because there has to be safety and you can't have a drug that you don't understand how it works or what the side effects are going to be. But things are really, I think, are appropriately quicker now to get to patients, which is great.

Alicia: And for the patient or caregiver, or anybody listening right now, and there are things they are asking themselves, "what's new in CLL research and treatment"? What would that be? Are there any exciting things out there that our listeners should take note of?

Dr. LaCasce: Yes; I mean, I think these combination studies, and there are a number of them. We have one here looking at combining venetoclax, acalabrutinib, which is

like ibrutinib, but, maybe less toxicity, with obinutuzumab in previously untreated patients with the goal of getting rid of any residual disease and stopping treatment. So that's the new thing. With combining drugs, you make deeper remissions and allow patients to come off treatment. So, that is one area that is exciting. I think CAR T-cells, you know, initially there—some of the early studies, at Penn, were in CLL patients and then you weren't hearing so much about CAR T-cells. It was looking at ALL or aggressive lymphoma. I think because all these novel drugs were coming into play, but now I think there is renewed interest in CAR T-cell because if that ends up being manageable, maybe that's less toxic than a donor stem cell transplant, an allogeneic transplant, so I think those are two big areas. There are some new other immune modulating drugs, I think, that are looking very interesting, like CAR T-cells but without having to genetically engineer a patient's own T-cells. So, I think there is a lot. There are many, many trials going on in CLL. It is very exciting.

Alicia: What about vaccine therapy?

Dr. LaCasce: So, vaccine therapy, that is something that is being looked at in a number of different cancers. I think we need to figure out in patients with CLL, their underlying immune system is not normal; so I think we would really need some good pre-clinical evidence to show that a patient with CLL can now take good response to a vaccine and what are the—you know, there are a lot of new generation vaccines trying to really try to personalize the targets for patients. So, it will be interesting to see—if that plays out.

Lizette: And with all these new combinations, and new and exciting treatments, and clinical trials, as well as better testing for minimal residual disease, do you think or anticipate that, in the future, instead of talking about CLL as being a chronic disease, do you think that there may be a possibility for a cure?

Dr. LaCasce: Yeah; I mean I think already we know that a subset of those younger patients who get FCR may be cured. We know that patients who have allogeneic transplants at the other end of the spectrum may be cured. If you can get someone to a minimal residual disease state, meaning you test in the blood or bone marrow and look to see if you can't find any CLL cells, we need to know—now follow those patients longitudinally. Is that because we just can't detect those cells and they are going to show up or, with combination therapies, are we really eradicating those cells? So, you know, and even if we can't eradicate them, but patients can have long disease-free intervals where they are off treatment, and living their lives, and have good quality of life, I think that is a really important goal as well.

Alicia: We touched upon genetics earlier, but I think that is something where I just wanted to mention again because it's something that I am reading more and more about and that sciences are learning more about the biology of CLL.

Dr. LaCasce: Yeah; so in terms of the mutations within the tumor cells, I think, as opposed to genetics, in terms of inheritance, is what you are asking. So yes we routinely get panels to look for TP53 mutations, those often go along with 17p and can be an indicator of a very difficult to treat disease. We want to know about that. There is NOTCH; there's SF3B1; there are a lot of mutations that are being identified that, may be important in terms of prognosis, but also in terms of choosing the optimal therapies. So, we do—here, we have a panel that we send and, I think, many centers have a panel that they send to sort of fully characterize the disease. Already, we are using cytogenetics and mutational status at the heavy chain genes, but some of these other mutations are extremely important in figuring out how to best manage a patient.

Alicia: It is an exciting time for a CLL patient.

Dr. LaCasce: It is! It really—it's you know—even since I have been doing this, it has changed so dramatically in such a good way.

Alicia: Yeah; thanks to physicians like you and researchers that helped to bring this all forward and educate other patients. A cancer diagnosis is never easy and I think when there is comfort in knowing that there (is) physicians like you that exist, that helps to say, "you know, there is somebody advocating for me." I mean, yes, self-advocation is very important, but to know that there is a team that is actively learning their field is a wonderful feeling as well.

Dr. LaCasce: And, you know, I think it is a community and, the providers around the country, and around the world, who focus on lymphoma and CLL, you know, now all know each other and, you know, learn from each other and design trials together so it is really, pretty great to be in—in that community and watch these things move forward.

Alicia: Absolutely. Well, thank you so much for speaking with us about CLL, Dr. LaCasce, and for all that you do for your patients. It has been great chatting with you and for anyone who is listening who would like more information about CLL, please visit www.lls.org/booklets for our CLL booklet as well as our CLL guide.

Thank you so much, Doctor.

Lizette: Thank you.

Dr. LaCasce: Oh; my pleasure. Great questions. Take care.