LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Breaking Down Primary CNS Lymphoma: From Rare Diagnosis to Growing Progress'

Description:

Primary Central Nervous System Lymphoma (PCNSL) is a rare form of non-Hodgkin lymphoma that affects the brain, spinal cord, or eyes. In this episode, Dr. Lakshmi Nayak of Dana-Farber Cancer Institute, helps us better understand this uncommon type of lymphoma. From early signs and symptoms to diagnosis, treatment options, and the latest clinical trials, Dr. Nayak breaks it all down in a clear and compassionate way.

Transcript:

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

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

Elissa: Today, we will be speaking with Dr. Lakshmi Nayak, the Director of the Center of CNS Lymphoma and Director of Clinical Research for the Center for Neuro-Oncology at Dana-Farber Cancer Institute in Boston, Massachusetts, as well as an Associate Professor of Neurology at Harvard Medical School. Dr. Nayak is actively involved in developing clinical trials in primary central nervous system lymphoma. Welcome, Dr. Nayak.

Lakshmi Nayak, MD: Thank you, Elissa and Lizette. It's a pleasure to be here to talk with you today.

Elissa: Well, thank you for joining us.

So, our episode today is on primary central nervous system lymphoma, also referred to as PCNSL and primary CNS lymphoma. Could you tell our listeners what that is?

Dr. Nayak: Sure. Primary CNS lymphoma is a very rare diagnosis. It's a rare central nervous system lymphoma, an aggressive type of lymphoma, mostly non-Hodgkin's lymphoma in type. And by definition when we say primary, it means that it's restricted to the nervous system or the central nervous system; and this comprises the brain, spinal cord, cerebrospinal fluid, and the eyes. And importantly, primary CNS lymphoma occurs in the nervous system in the absence of systemic disease. So, at the time of diagnosis, patients do not have any evidence of systemic lymphoma and that makes it primary by definition.

Elissa: So, what is the difference between primary and secondary CNS lymphoma?

Dr. Nayak: I'm glad you asked that. So, secondary CNS lymphoma refers to lymphomas in the nervous system that develop as a result of existing lymphoma in the body or systemic disease.

These can occur in three different scenarios. The first scenario could be at the diagnosis of systemic lymphoma, so both, systemic lymphoma and CNS lymphoma occur concurrently. And then occasionally, patients can develop what we call CNS relapse, so those that have systemic lymphoma were treated with chemotherapy for their systemic disease were in remission and then had a relapse in the nervous system. And then sometimes, rarely, we can see patients develop CNS and systemic lymphoma at the time of relapse of the systemic disease, so three different scenarios, but again occurring as a result of systemic lymphoma is secondary CNS lymphoma.

Lizette: And I know that you mentioned that primary CNS lymphoma is a rare type of non-Hodgkin lymphoma. So, what makes it different than the other non-Hodgkin lymphomas?

Dr. Nayak: So, primary CNS lymphoma, most of them are non-Hodgkin lymphoma. About 90% or so are diffuse large B-cell lymphomas that are the more aggressive types of systemic lymphomas. And then, less than 10% include T-cell lymphomas or follicular lymphomas, marginal zone lymphomas, and other types of low-grade lymphomas. For the purpose of this discussion, what we will talk about is the primary CNS diffuse large B-cell lymphomas.

Additionally, while we're on that topic of how does it differ from systemic diffuse large B-cell lymphoma, historically, we used to think of primary CNS lymphoma of the diffuse large B-cell subtype as to be quite indistinguishable from systemic lymphoma itself because under the microscope or what we call onco- histopathology, it looked the same.

However, now we recognize that with comprehensive genomic analysis when we do additional genetic testing of the tumor itself, we have found that this is actually quite a distinct disease with unique targets. And we also recognize now how it behaves differently and more aggressively and less response to certain types of chemotherapies compared to systemic lymphoma.

Elissa: So, what are common signs and symptoms of primary CNS lymphomas? What might bring someone to the doctor to be diagnosed?

Dr. Nayak: So, interestingly enough, signs and symptoms of brain tumors can mimic signs and symptoms of anything going on in the brain. There's no sign or symptom specific to primary CNS lymphoma. Really, the symptoms depend on the location of the brain that is involved. But what we have seen is most patients do present with some memory changes, cognitive disorders that can progress quite rapidly, not slowly over years, but over a period of weeks. Some patients can have language disorders. Some patients can have weakness of the arm or leg. Gait abnormalities or difficulty with walking is also something that is noted in about 50 to 60% of patients.

And so, we generally say that if there are any new symptoms, neurologic symptoms that developed over a course of weeks and that are progressively getting worse, it's probably important to see the neurologist or a primary care doctor or get a CAT scan or an MRI to have further evaluation.

One thing to mention is that this disease is not uncommon in older people; and so oftentimes when patients do have cognitive disorders or symptoms such as memory changes, these can be misdiagnosed; and so we suggest that if there's a rapid change, you know, if someone was perfectly fine and then seemed to be different over a matter of weeks, it's probably a good idea to get evaluation sooner than later because it may not necessarily be a memory disorder. It may be something else.

Lizette: Wow. And are there any predispositions or any kind of risk factors that might make it more likely for someone to be diagnosed with primary CNS lymphoma?

Dr. Nayak: These tumors are quite rare. They occur in about 1,500 to 2,000 patients every year in the US alone. So, not a very common disease. As such, we haven't found any risk factors that are defined for what we call immunocompetent primary CNS lymphoma. However, there's a condition called immunocompromised primary CNS lymphoma; and this is what occurs in patients, as the name suggests, that are immunocompromised.

In the 1980s, we saw an increase in the incidence of such lymphomas in younger patients; and this was related to the HIV/AIDS epidemic. However, in the 1990s and 2000s, when these infectious diseases were under control and the incidence of AIDS went down substantially because of good control with the drugs, this incidence of immunocompromised primary CNS lymphoma went down substantially. Nowadays, we do see patients with immunocompromised primary CNS lymphoma, and those are patients who have had a history of organ transplant that are on long-term immunosuppression and also patients who have autoimmune diseases that are on long-term immunosuppressants.

But it's important to note that the risk of developing primary CNS lymphoma in the context of these immunosuppression is very, very low. So, it doesn't mean that every patient or a majority of patients with these disorders will get primary CNS lymphoma. The risk-benefit ratio is always looked at in these cases. So, this is not to scare people who are on immunosuppressants. Of course, it's extremely rare even in that population.

Elissa: Now, you've mentioned several times now that it's very rare, it's a very low risk of getting this. So, what is the overall incidence rate of primary CNS lymphoma?

Dr. Nayak: So, in the US, it's about 1,500 patients yearly. The incidence is a bit higher in older people, so those that are over 65, the incidence increases slightly. But overall, it's quite a low risk as you can imagine when it compares to other cancers.

Elissa: So, could you tell us about the staging for primary CNS lymphoma? Does the staging affect prognosis and then determine the treatment?

Dr. Nayak: So, primary CNS lymphoma, as a reminder, is restricted to the brain. When you think of lymphoma staging, it comes under Stage 1E because it's in only one organ, and it's an extranodal organ. So, in that regard, it doesn't sound that it's very aggressive, right? We don't stage primary brain tumors typically. What we do is we look for what is called "Extent of Disease" (EOD) evaluation. And so, whenever we see a patient that has a brain tumor and the biopsy-confirmed diffuse large B-cell lymphoma, we would like to confirm that it is, indeed, a primary CNS lymphoma.

So, for that, we would check a CT scan of the body or a PET scan of the body to confirm there's no systemic disease. In older men, we recommend getting a testicular ultrasound because testicular lymphoma is associated with CNS relapses and a high association with that. So, we'd like to rule out testicular lymphoma as well.

And then finally, we'd like to see what compartments of the nervous system are involved. Is it just the brain where we saw the brain tumor on the MRI? What about

the spinal cord? What about the spinal fluid? And then, of course, what we call the vitreoretinal space or the back of the eye. And these spaces or compartments of the nervous system need to be checked for Extent of Disease evaluation.

It's important because not just because it gives us an idea of what different locations of the nervous system the disease is in. We generally think of primary CNS lymphoma as a whole brain or a whole CNS disease, regardless of what location we see it in in the brain. But, when we're looking at responses of treatment, at the end of treatment we want to make sure that if, for example, the eye was also involved in addition to the brain, then that is also checked for along with an MRI to make sure that every compartment of the nervous system is free of disease at the end of treatment.

Lizette: Now, just getting to treatment. So, it seems like a different type of lymphoma because it is the central nervous system. Are the treatments for primary CNS lymphoma very different from other types of lymphoma?

Dr. Nayak: That's correct. The treatment for primary CNS lymphoma is very different from systemic lymphoma. For systemic lymphoma, the standard of care is to use R-CHOP and nowadays, some additions based on the stage of disease itself. What is noted is that the brain and the nervous system keeps itself separate, and so, there is this concept of what is called the blood-brain barrier. And what we noted was that chemotherapeutic agents did not penetrate well enough to give good responses in the nervous system.

And so historically, primary CNS lymphoma was treated with radiation. However, in the 1990s, we noted that a drug called methotrexate, when given in high doses, hence called high-dose methotrexate, increases responses. And when combined with radiation, leads to better remission-free and disease-free survival. And so now, over several years with several studies that have been conducted, we now noted high-dose methotrexate-based chemotherapy is the best initial treatment for this disease. So, we definitely know that high-dose methotrexate forms the backbone of all

chemotherapeutic regimens. And then, we also know that adding a drug called cytarabine in high doses also leads to better response rates.

Additionally, many regimens use types of chemotherapy called alkylating agents as well. For example, in our center, we use temozolomide, which is an oral chemotherapy pill which is known to penetrate the brain. Some other centers use procarbazine, which is also an alkylating agent and also known to penetrate the brain.

And then rituximab has been increasingly used in primary CNS lymphoma regimens as well; and much of this came from its use in systemic diffuse large B-cell lymphoma where it was shown to have significant improvement in response rates and survival. And some studies have shown that the addition of rituximab is favored in addition to high-dose methotrexate-based chemotherapy, as well.

The treatment is divided into two phases or stages. The first part is induction. Induction therapy, its role is really to achieve what we call a complete response. That means we'd like to eradicate all evidence of the tumor. And so, this chemotherapy regimen that I was referring to forms the basis of what is called induction chemotherapy.

At the end of induction chemotherapy, we expect for patients to have a complete response. However, we do know that even in patients that have a complete response, the risk of recurrence for the tumor to come back is quite high, and it's about 50% at about two years. And so, we have been trying to look for additional treatments to prevent the risk of recurrence. Traditionally, whole brain radiation after induction chemotherapy was used. But, we now know that the combination of chemotherapy and radiation does increase the risk of what we call neurotoxicity. This means that patients tend to have a good response and oftentimes they may not have recurrences. But the longer they live, the higher their risk of side effects seems to occur.

And these side effects are typically in the form of memory problems, difficulty in attention, and gait problems. And unfortunately, there's not much that we can do to

change these symptoms once they occur. These symptoms are often progressive, and as you can imagine, lead to a significant amount of morbidity.

And so, for several decades now, we have been looking into, what can we do to prevent such side effects? And so, therein comes the next type of consolidative treatment that we'll talk about, which is high-dose chemotherapy with autologous stem cell rescue. And now, based on several studies that have looked at high-dose chemotherapy with autologous stem cell rescue, either by itself or comparing it with radiation, or comparing it with chemotherapy alone, we now know that in patients that are considered to be favorable candidates for an auto transplant, we will offer it to those patients because the risk of progression-free survival, that is the time taken for the disease to return or come back, and also the risk of overall survival is significantly reduced when patients are able to complete induction chemotherapy followed by consolidation with auto stem-cell transplant.

Lizette: Now, I know that the goal for treatment is different between different types of non-Hodgkin lymphoma. So, for the aggressive forms, the goal of treatment is to cure. And for the more chronic forms, it's more to manage the disease. They tend to come back. So, for primary CNS lymphoma, the goal is to cure?

Dr. Nayak: So, I hesitate as a neuro-oncologist in using the word "cure," but I have to say that seeing patients being treated with primary CNS lymphoma over almost two decades, I've seen that practices have changed and we do have significantly increasing numbers of long-term survivors.

When we're talking about treatment options with patients, I discuss it with them in terms of different timepoints. So, the first timepoint I always say is the two-year landmark because the two-year timepoint, is the highest risk of recurrence that patients are going to recur, they'll recur within the first two years. The second timepoint is five years, and I think mostly when patients get to five years, the risk of recurrence goes down substantially. And then the next timepoint is ten years.

The question really is if it did occur after ten years, was it the same disease or something else? In fact, a long time ago, I had looked at this question with some of my colleagues at MSKCC (Memorial Sloan Kettering Cancer Center); and we found that the same clone was found in patients that had recurred even 13 years later. So that just speaks for how these tumors can behave. But going back to your point, I think that we are in the time where we can offer long-term remission for many patients.

Lizette: That is good to hear. I know that we hear different terms out there. I know that I've heard BTK (Bruton Tyrosine Kinase) inhibitor, CAR T-cell therapy, bispecifics. Are all these treatment options for this type of lymphoma?

Dr. Nayak: So, after we were able to identify primary CNS lymphoma as a distinct disease based on the genomic analysis, what we did find that primary CNS lymphoma exhibits mutations that can be targeted. And since you mentioned BTK inhibitors, I'll first start with the role of BTK inhibitors in primary CNS lymphoma because this has been the most extensively studied type of treatment in the context of novel treatments in primary CNS lymphoma.

So, ibrutinib is the first-in-class oral BTK inhibitor that was investigated in relapsed and refractory primary CNS lymphoma initially. The responses rates were extremely good, in some studies even up to 70%. But in Cooperative Groups studies, about 50% or so. What we noted though that by itself, the responses were there, but they were not durable. Nonetheless, it was very exciting for us to see the initial responses with the BTK inhibitors, and we also noted that overall the response of BTK inhibitors in primary CNS lymphoma was much better than what was seen in diffuse large B-cell lymphoma or systemic lymphoma for that matter. And this was truly related to the genetics of the disease, which is more predominant in primary CNS lymphoma.

And even though as a single agent, the majority of the patients developed resistance mechanisms and do tend to recur and relapse, this led to further combinations of studies, as well as investigating this in what we call upfront regimen. Can we add BTK

inhibitors to high-dose methotrexate-based regimens and see if we can get better responses or not?

At this timepoint, there are several other next-generation BTK inhibitors that are currently being investigated, drugs such as tirabrutinib, acalabrutinib, zanubrutinib. There are studies that have been recently completed or will be completed in the next year or so. And so, we're excited to see where these drugs will really fit in.

There's a group of patients that tend to respond a bit better and have long-term durable responses. We're looking to identify and see which patients are those that have long-term responses; and again, like I mentioned, see if we can bring these drugs in the upfront setting because one thing to remember is that this disease impacts the brain. And every time it recurs, there's more damage to the brain as a result of the disease itself, not just in terms of impact of the treatment.

And so, it's best for us to be able to try to eradicate it the first time around so that people can recover their neurologic function and then, can live longer lives but be able to do whatever they used to do for their life – you know, be able to go work, not be cognitively impaired and really be able to live full lives. And so, the goal of myself and many investigators is really to try to see what we can do, not just in the recurrent setting, but how can we bring all of those in the upfront setting?

Perhaps, maybe we'll talk about the CAR T-cells.

So, CD-19-directed CAR T-cell therapy has, of course, revolutionized the treatment of systemic diffuse large B-cell lymphoma. And one of the side effects that was noted when these drugs were being investigated was neurotoxicity, also called ICANS or immune cellular therapy-associated neurologic syndromes or toxicities related to that. And so, in all of those initial studies that led to the FDA approval of CAR T-cell therapy, in systemic diffuse large B-cell lymphoma, CNS lymphoma patients were excluded.

One of the reasons that CAR T-cell therapies were excluded in primary CNS lymphoma patients was a result of the toxicities that were noted; and as we investigated these toxicities, we were able to demonstrate that CAR T-cells actually were present in the spinal fluid or were penetrating the nervous system. The question was that if there is neurotoxicity noted in patients that don't even have brain tumors, what would it be like to treat patients that have brain tumors? Would we encounter more side effects and more neurotoxicity?

And so initially, there were pilot studies that were conducted. One was conducted by our group. Another one at another center, also in Boston, and we were able to show in our initial studies that, in fact, not only are CAR T-cell therapies safe in primary CNS lymphoma patients, but they're also found to be quite efficacious. And a good number of patients actually have very good durable responses.

With this now, there are larger studies being conducted to see how these therapies are in a larger group of patients, of course. And again, like I mentioned, how can we move this in the upfront setting? How can we try to utilize this?

So, for that, I'll just segue back about the transplant piece. We talked about how patients that can get chemotherapy with autologous stem cell transplant tend to do really well. But this type of therapy, as you can imagine, is favorable only for a small number of patients – those that we call transplant eligible.

The majority of patients that we do encounter are over 65. So, only a small fraction of those patients can actually undergo heavy duty chemotherapy and all of the toxicities that could result as a result of the transplant regimens. And for this reason, we're trying to see what can we bring into the upfront setting for consolidation; and now there are several studies that are investigating the role of CAR T-cell therapy for consolidation after achieving a response in a primary CNS lymphoma patient. And I think if we show that this actually seems to increase the durability of the response and remission, and disease-free interval, this will make a huge difference for our patients.

Lizette: And is there anything with bispecifics, since we keep hearing the term "bispecifics" for a lot of our lymphomas?

Dr. Nayak: So, there have been some studies that are now looking at bispecific antibodies and in primary CNS lymphoma too. The published data is currently what I call retrospective. In general, the way I look at it is that, we now understand a lot more about brain tumors and primary CNS lymphoma in terms of the genetics, the genomics. We're also getting much better at developing molecules that can penetrate and cross the blood-brain barrier. And in the form of T-cell therapies or using immunotherapies, we also know that these can cross the blood-brain barrier and seem to have a different approach from a mechanism standpoint compared to our traditional chemotherapy, which didn't work very well in the nervous system.

So, I think at this time this is a very exciting period. In general, of course, for oncology and in the lymphoma world with the number of treatments that we are seeing for systemic lymphoma too; but also, for primary CNS lymphoma, the number of trials have substantially increased. And I think that in the next ten years, we will probably be ready to change our guidelines into what is truly standard of care.

Elissa: Okay. So, you mentioned a couple side effects and then toxicities that could come with treatment. What are some other side effects that patients might experience from these treatments, and are these side effects manageable?

Dr. Nayak: Perhaps since we talked about chemo and the radiation side effects, what we could talk about is side effects from targeted therapies and side effects from CAR T-cell therapy. So, if you take, for instance, BTK inhibitors, the common side effects that are encountered are that platelets that are cells in blood can drop down. And in brain tumor patients, this is something to monitor a bit more carefully because brain tumors can be predisposed to bleeding. So, the risk of bleeding becomes slightly different when the platelet counts go down and need to be maintained at a slightly higher level than otherwise.

And then, the risk of infections is also higher with BTK inhibitors, and sometimes as we're combining these with chemotherapy regimens. It's important to note whether we're further increasing the risk from the myelosuppressive component of the chemotherapy in combination with the way the targeted therapies work. And so, we have to pay attention to how people are doing with the risk of infections.

Many of these treatments also can have side effects in the form of skin rashes. Drug-related skin toxicities are not uncommon with novel agents, but the risk can be quite high in the BTK inhibitors. Of course, most of these are quite manageable with creams, and most people don't really have the dangerous side effects from skin toxicity that requires them to go to the hospital. But, when the patients do develop some itching of the skin, it's probably a good idea to keep a close eye on how they are progressing.

And then, some of the BTK inhibitors have been noted to increase some cardiac rhythm abnormalities and develop atrial fibrillation, and so those are things to look into. If patients develop palpitations or so, they should seek attention a bit sooner to make sure that they're taken care of and their cardiac rhythm is normal.

And with regard to CAR T-cell therapies, you know, these are genetically engineered T-cells. At this time, when we do give CAR T-cell therapies in the context of our trials for primary CNS lymphoma patients, patients are admitted and watched for a period of at least seven days. And if they're feeling well at the end of seven days, they're discharged.

What we're really noticing and monitoring for are the common side effects that are associated with the CD19-directed CAR T-cell therapies which are mostly what are called CRS or cytokine release syndrome. These can occur within three to four days of administering the cells. And this can manifest in the form of high fevers, chills. Sometimes patients can have difficulty breathing, their blood pressure might drop, and sometimes patients need to be monitored in the ICU.

Again, I think we're getting much better at monitoring and treating these side effects as we gain more experience with CAR T-cell therapy, and there is development of CAR T-cell therapy with fewer side effects now as the compounds are changing and evolving.

After about five to seven days, we can notice the neurotoxicity or ICANS. These could be as simple as headaches, some mild confusion. Some patients have trouble with language. And then, other patients can go into a coma and may need to be monitored in the neuro ICU in this case. So, these don't last for more than a few days and again, we have better treatments to manage these. Of course, these treatments need to be given in the context of institutions that have the support system to manage all of these side effects.

And then, for the purpose of most of these therapies, we do ask patients to report to us if, within the next few days after discharge, they're having any side effects and come present to the emergency room right away.

And then, in terms of delayed side effects from CAR T-cell therapy, some patients can develop some decrease in blood cell counts, so, we monitor for those and see if they require an immunoglobulin, a support, or so on and so forth.

Lizette: Now, I know that you've been treating primary CNS lymphoma for a long time. What are you excited about right now about any new or emerging treatments?

Dr. Nayak: I'm excited about the fact that, when I first started as faculty, I could only give chemotherapy; and now I have a whole menu of trials for patients that, we start with one, and if that doesn't work very well, we go to the next one and then the next one. And honestly, as a neuro-oncologist, to be able to see increase in survival and being able to offer the next treatment and the next treatment and the next treatment makes me very happy that we're definitely making a significant amount of progress.

I am certainly very excited about immunotherapies, including cellular therapies and, of course, targeted therapies as well, along the lines of what we call the B-cell receptor signaling pathway, which includes not just BTK inhibitors but others that we're using in combination like now with an IRAK4 inhibitor We're also doing a tremendous amount of work in understanding the biology of the disease and mechanisms of resistance with targeted therapies as well as with cellular therapy that will then help us identify which patients do better, which patients can we combine certain treatments with, how do we counteract those? So, as I said earlier, I think that we will be looking at a change in the paradigm of this disease in the next ten years or so.

Elissa: That's great.

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

Dr. Nayak: I first start by saying that time is brain. We use that term with strokes. There's a lot of press about if you have signs of a stroke, go to the emergency room right away.

I think it's the same for primary CNS lymphoma in a way. This is a very treatable disease. I think that we are very close to making this a curable disease for most patients. And, I don't think that we could have said that in the same way before, but now we can. And so, patients sometimes can look very sick and have significant effects from the tumor. And it feels like, how can they even get better? How can they be themselves?

But we see after we institute treatment that people actually do better, and they're able to do all of the things that they could before – go to work, those that couldn't speak very well could start speaking. Neurologic symptoms reverse when we treat people with primary CNS lymphoma quickly enough, and now we're able to control the disease and aim for a cure.

Elissa: That is wonderful. We love to hear that, and so thank you so much, Dr. Nayak, for joining us today on the podcast and telling us all about primary CNS lymphoma. We really appreciate you coming on with us today.

Dr. Nayak: Well thank you for having me. It was a pleasure.

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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