LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'How New Therapies Are Changing The Future of Myeloma'

Description:

Remarkable progress has been made in the treatment of myeloma over the past decade, giving patients and families much hope for the future. In this episode, we speak to Dr. Nishi Shah of Montefiore Einstein Comprehensive Cancer Center in New York City. While the wide variety of therapies available to patients are discussed, this episode also focuses on the newest, cutting-edge therapies for myeloma, such as CAR T-cell therapy and bispecific antibodies.

Transcript:

Elissa: Welcome to *The Bloodline with LLS*. I'm Elissa. Thank you so much for joining us on this episode. Today, we will be speaking to Dr. Nishi Shah, a hematologist/oncologist at Montefiore Einstein Comprehensive Cancer Center in New York City. As a clinician and clinical investigator, Dr. Shah focuses on plasma cell disorders, including multiple myeloma. Much of her work is concentrated on improving access to care and addressing gaps in clinical knowledge, health equity for myeloma patients, and exploring methods to improve patient access to clinical trials. Welcome, Dr. Shah.

Nishi Shah, MD: Thank you so much for having me, Elissa. It's my pleasure.

Elissa: So, our episode today is on multiple myeloma. Could you explain to our listeners what that is?

Dr. Shah: Sure. So, multiple myeloma is a blood cancer of a particular kind of white cells called plasma cells. We all have plasma cells. These are B white cells that help make antibodies to fight infection.

So, in multiple myeloma, these plasma cells have undergone certain genetic mutations and are multiplying more than they should be, leading to a cancerous growth. It is the second most common blood cancer that we have in the United States currently.

Elissa: So patients listening may also have smoldering myeloma or MGUS. Could you explain those as well?

Dr. Shah: Sure. So, what we see in multiple myeloma is that these abnormal plasma cells that have become cancerous are making aberrant antibodies that can be detected with certain bloodwork. So, smoldering multiple myeloma and monoclonal gammopathy of undetermined significance called MGUS, these are two more disorders on the spectrum. So, usually these are considered to be a precancerous state. Typically, any patient with multiple myeloma had an MGUS at some point, and what we see is that there is only a small amount of abnormal protein detected in the blood for those group of patients.

Smoldering myelomas falls somewhere between MGUS and multiple myeloma where we see a bigger clone of those plasma cells that have become abnormal but not enough to cause any organ damage to the patient. And these patients are typically either taken to a clinical trial or if some of them have high-risk features, can be considered for certain therapies or just watched very closely.

Elissa: Now, do they always turn into multiple myeloma, or are there some cases where they could live their whole lives with smoldering myeloma or MGUS and not have it turn into myeloma?

Dr. Shah: That's a great question. So, for MGUS, typically, there might be a lot of patients who will just live with MGUS for their entire life. We use certain blood labs to determine the prognostic features for a particular patient. In terms of smoldering myeloma, there is a higher chance of these patients progressing to symptomatic multiple myeloma requiring therapy. But even in that group of patients, there may be some patients who will probably just have smoldering myeloma all their life.

Myeloma is typically a disease of older individuals, so it's certainly possible that this was detected incidentally; and patients may have other conditions that lead to their death rather than smoldering myeloma.

Elissa: How does myeloma develop? Are there certain factors that may increase the likelihood of getting myeloma?

Dr. Shah: The way I explain to my patients is in most of the patients that I have, I cannot say that, "Hey, this is the reason why you've developed multiple myeloma." Certain genetic or environmental factors in that particular patient may predispose them to develop cancer. What we know is that certain chemical exposures have been associated with a higher incidence of multiple myeloma. For example, agent orange is known to have a higher association for developing multiple myeloma. Patients who are overweight could also be at higher risk of developing multiple myeloma, but what was the basis for these particular risk factors that lead to these patients developing multiple myeloma is still unknown and being studied.

Elissa: Now, we know that African Americans are at greater risk of getting myeloma than others. Do we know why that is?

Dr. Shah: We do not have any particular etiology that we can attribute to the cause, like why African Americans have a higher incidence of multiple myeloma. We know that the incidence is twice as much in African Americans than in Caucasians. There is no causative factor that we have identified at the moment.

Elissa: Okay. Now, you mentioned that myeloma is a pretty common blood cancer. What is the prognosis for myeloma patients?

Dr. Shah: So, based on the last SEER (Surveillance, Epidemiology and End Results Program) five-year estimates for overall survival, which is a bit old at the moment, like 2015 to 2019. I would say that five-year overall survival is close to 60%. But having said that, more and more patients are living longer with multiple myeloma given the

new therapies that we've had in the last couple of years. And I'm sure that more and more patients will be living longer, and the five-year overall survival for the next estimate that we get will be even higher.

Elissa: That's really good, and we'll get into treatments in a moment. But it's good to hear that the prognosis is definitely getting longer for patients.

Now, what are the common signs and symptoms of myeloma? What brings patients into the doctor prior to their diagnosis?

Dr. Shah: So, typically, in myeloma, what we see is that these abnormal plasma cells are multiplying and infiltrating the bone marrow. So, with the infiltration of bone marrow, there are less of the normal cells in the bone marrow; and patients are usually anemic. That may lead to weakness, fatigue, and bring them to a doctor.

We have quite a few patients who, they go to their PCP and are found to be anemic; and on further investigations, we find that they have an abnormal monoclonal protein and are sent to hematologists for further evaluation. So, anemia is one common way of diagnosing multiple myeloma. There are some patients who may present with kidney failure, or it could be in the form of just mild abnormality in their kidney function; or there are some patients who present at the brink of dialysis. That could be one way of diagnosing multiple myeloma. There are some patients who present with bone pains, and that could be another way of diagnosing myeloma.

Elissa: With the bone pain, and some patients can even have fractures, why is that associated with myeloma?

Dr. Shah: So, in myeloma, we see infiltration of the bone marrow by the plasma cells. So, that leads to destruction of the normal bone. These abnormal plasma cells produce certain factors that tip the balance of the bone towards destruction rather than growth. So, there are more cells that are destroying the bone rather than forming the bone.

So, we see that happen in any bone potentially in myeloma patients, so they are at a higher risk of fractures. We see these abnormal myeloma cells. They will develop these lytic lesions that we see on the x-ray or on their imaging, and that's how we know that this appears to be myeloma.

Elissa: So, since we were talking about treatments creating a longer prognosis, what are the current treatments for myeloma?

Dr. Shah: I'm happy to say that we have numerous treatments that are available for multiple myeloma. Typically, we start a newly diagnosed patient with multiple myeloma with a four-drug or a three-drug combination of particular classes of drugs. So, one such class of drugs is called immunomodulatory agents or IMiDs. There are two drugs that we typically use, Revlimid® and pomalidomide. Revlimid's other name is lenalidomide. These are both oral pills that our patients are given for treating their multiple myeloma.

The second class of drugs are proteasome inhibitors. There are three different drugs in this category. One is called ixazomib, one is called bortezomib, and the third one is called carfilzomib.

The third big class of drugs in myeloma are monoclonal antibodies that target CD38 on the multiple myeloma cells. It's a protein expressed on the multiple myeloma cells, so there are antibodies that particularly target myeloma cells because these antibodies target CD38 on the myeloma cells.

So, there are two drugs in this class, daratumumab and isatuximab. And almost all patients of myeloma will be given a combination of these drugs with steroid, usually dexamethasone.

And say a patient walks into my clinic with a new diagnosis of multiple myeloma, the first thing that I think about for that patient is whether this patient is eligible for an autologous stem cell transplant or not. And my treatment will probably change,

depending on the functional status of the patient, the other organ involvements or other comorbidities that my patient has.

So, stem cell transplant with melphalan as their chemotherapy backbone is one of the oldest treatments that we have for multiple myeloma, and it's a very effective treatment that we still offer to some groups of patients who may benefit.

Elissa: Could you explain what an autologous transplant is?

Dr. Shah: Sure, so typically how I explain to my patients is that what we are trying to do is give you high dose of chemotherapy that's going to just wipe out your entire bone marrow, including the myeloma cells and normal bone marrow. So, those stem cells that we collect from patients prior to giving them this chemotherapy are given back to the patient after they get melphalan to help grow the normal bone marrow but at the same time get rid of the myeloma cells altogether. So, essentially, autologous stem cell transplant can be thought of as a stem cell rescue, but patients' own stem cells will rescue their bone marrow after getting melphalan.

Elissa: Now, in addition to all of those treatments and autologous transplants, what about CAR T-cell therapy? Are myeloma patients eligible for that?

Dr. Shah: Yes, absolutely. There are two FDA-approved CAR T-cell therapies for multiple myeloma patients. Both of these CAR T-cell therapies target a particular protein on the myeloma cell called B-cell maturation antigen, BCMA. The two CAR T-cell products, I'll just the short names instead of the long names. Those are ide-cel or idecabtagene autoleucel, and the second is cilta-cel or ciltacabtagene autoleucel.

Elissa: A treatment that patients are starting to hear more about is bispecific antibodies. You mentioned monoclonal antibodies earlier. Could you explain what bispecific antibodies is and how it's used to treat myeloma?

Dr. Shah: Absolutely. So, bispecific antibodies, how I explain to the patients is that it's basically a drug where there are two arms. One arm connects to CD3 on the

patients' T-cells which are immune cells in the patient's body, and the other arm connects to the myeloma cells.

There are two targets that the bispecific antibodies have. One is BCMA, just like the CAR T-cell, which is B cell maturation antigen. There are two FDA-approved bispecific antibodies that target BCMA. One is teclistamab, and the second one is elranatamab.

The other bispecific antibody for myeloma that is approved is called talquetamab. It targets a different antigen on the myeloma cell which is called G protein-coupled receptor class 5. It's a handful. It's class C group 5 and member D. So GPRC5D. It's a different target on the myeloma cell. So, there are three FDA-approved bispecific antibodies, and essentially it's building the patient's own white cells to target the myeloma cell.

Elissa: Okay, so just so patients listening may understand, you're saying that the bispecific antibody has two arms, one connects to the patient's T cells and the other to the cancer cell. That then helps the T cell to attack the myeloma cell. Is that correct?

Dr. Shah: Yes, absolutely. So, it's using the patient's own white cells to destroy the myeloma cells. Essentially, the patient's own immune system to kill the myeloma cell.

Elissa: Has that been very effective?

Dr. Shah: Yes, absolutely. These therapies have definitely helped our patients live longer and have improved the response rates for multiple myeloma.

I'll give you just an example. I had a patient about two years back. I had started here as a faculty just less than six months into my practice, and I had inherited this patient from a colleague of mine. She was 59 years old and had seen all the therapies that I could offer for her. But I saw that her myeloma was getting worse. At that time, we had only heard and seen clinical trial results in meetings for these bispecific antibodies.

We worked on getting one of these products for her on a compassionate use because really if it wasn't for that, I didn't have anything else to offer. And she lived a year longer after getting one of these therapies, and when she progressed on that therapy, I got this other approved FDA bispecific for her; and she's still alive and with me and responding very nicely to her treatment.

So, if it wasn't for these newer therapies, our patients like her would have nothing that we could have offered. But I can say that these are durable responses and typically very well-tolerated treatments.

Elissa: That's wonderful to hear. You mentioned that she'd been through quite a lot of treatments. Are bispecific antibodies ever used as a first-line treatment?

Dr. Shah: So, at the moment, FDA has approved these therapies for patients who have had four or more prior lines of therapy for multiple myeloma. As we know, multiple myeloma is not a curable illness, but it's highly treatable. So, typically patients will respond to one line of therapy. At some point if they stop responding, they go onto a second line of therapy and so on and so forth.

So, patients who have been through four different lines of therapy are the ones who are currently FDA approved to get these treatments. But there are studies ongoing to evaluate whether there is a role for these bispecific antibodies earlier in the therapy, say second line, or as part of their first-line therapy as well.

Elissa: So, what are side effects of bispecific antibodies?

Dr. Shah: It depends on the kind of bispecific antibody that a patient gets. So, for teclistamab and elranatamab, the B-cell maturation antigen, we have different set of side effects than patients who get talquetamab. So, for teclistamab and elranatamab, we have seen some infections that occur in this group of patients. We are very mindful of the infectious complications that could develop.

So, some of these infections include viral infections such as COVID or other upper respiratory viral infections. In addition, there are some patients who may develop or reactivate their CMV infection. CMV is cytomegalovirus. So, infectious complications is something we watch out for, more the BCMA targeting bispecific antibodies than the other ones.

The second group of complications that we see with this therapy, as so we do with other therapies, is slight changes in their white count, their platelets, or the hemoglobin. Those could go down with the treatment, and we may need to give them growth factor support or a platelet transfusion, occasionally blood transfusions.

The third set of side effects that we see with, actually, all the bispecific antibodies and, similarly, with CAR T-cell therapy is called, there are two in this category: immune side effects, which is cytokine release syndrome and neurotoxicity. So, how I explain to my patients is that cytokine release syndrome is when, as your body's T-cells are engaging with the myeloma cell and trying to kill the myeloma cell, they release by-products that can cause symptoms such as fever, shortness of breath, or blood pressure changes.

So, we watch out for this group of infections; and this infection, given our experience with CAR T-cell therapy where these side effects could be quite difficult to manage, we require that patients get hospitalized for their bispecific antibody therapy. That's what FDA has recommended for all patients who get bispecific antibodies to get admitted.

Elissa: How long do they get admitted for?

Dr. Shah: So, typically, for bispecific antibodies, we would be admitting them and giving them smaller doses in the beginning. We give them what we call step-up doses. There are two to three step-up doses, depending on the drug.

For example, say I admit a patient today, I would give them a smaller dose of the drug that is in the hospital. We watch them for about two days where we see if the patient has any fevers or any blood pressure changes or any oxygen requirements. If they're

doing fine, typically, at the end of two to three days, we give them a slightly higher dose, the step-up dose 2. Again, if they are doing fine after the second step-up dose at two to three days interval, they get their third dose. So, they typically are in the hospital for close to seven days.

Things may change in the future. There are certain places in the country where not everybody is getting hospitalized but are just coming to the clinic day in and day out and staying there for close to 12 to 13 hours. And like where they're observed, and, but they can go back home. But in most places at the moment, patients get hospitalized to get their bispecific therapy.

The second one is neurotoxicity where patients could develop side effects such as confusion, dizziness, and at the worst in the spectrum seizures or altered mental status. That is thought to happen because, again, as those T cells or the immune cells are engaging with patients' myeloma cells, these by-products that are released can cause potentially swelling in the patient's brain or cause some edema there; and that is thought to be the reason for these side effects. Typically, these side effects can be managed very well, and it happens in a small proportion of patients.

All the places that offer bispecific antibodies, there are nurses, and all the staff, physicians as well as advanced practice providers have all been trained to watch out for these side effects and to treat them as needed.

So, whenever I admit a patient for these bispecific antibodies, I tell them that we're going to be asking you a bunch of silly questions every nurse shift to make sure that they are not confused, that they are able to answer the question properly. They are able to write properly and do mental math. So those are some of the things that we look out for.

For the third drug, talquetamab, there are some unique side effects where patients can have change in their taste sensation and may have some skin changes that we see as they start their therapy in the initial first month of therapy. These are thought to

happen because the target for the medicine called talquetamab is also present on skin, hair follicles, and the taste buds on their tongue.

So, I have some patients who are losing their sense of taste. We have come up with certain solutions for this, including reducing the frequency of the drug administration with time or reducing the dose of the drug to help mitigate the side effects. But these are some of the side effects to watch out for.

Elissa: Are there any longer-term side effects that patients need to be aware about?

Dr. Shah: So, long-term side effects with the bispecifics, I would say infectious complications, are short term as well as long-term complications, are something always to be aware of.

One thing we have been doing is giving IV immunoglobulins to patients every month or so to help reduce the risk of infections. So that is one thing. Talquetamab-related taste changes can sometimes stay for longer than a month also.

Those side effects of taste change can also improve with time with these modifications in drug dose as well as drug frequency.

Elissa: All right, so now that we've talked about current treatments, let's talk about emerging therapies. Are there any emerging treatments or clinical trials that you're particularly excited about?

Dr. Shah: Absolutely. There are many different trials ongoing in multiple myeloma. And for me, I can think of different ways in which to answer this question. One is that we are trying to evaluate the role of these novel therapies such as bispecifics, CAR Ts in an earlier line of treatment. We have a trial coming up at Montefiore Einstein Comprehensive Cancer Center where we are trying to offer patients CAR T therapy instead of autologous stem cell transplant as part of their first-line treatment.

So, trying to evaluate the role of CAR T cells early on and assessing how different would the response be as compared to say a patient who gets a transplant is what we are trying to study. There are certain therapies where we are trying to incorporate bispecific antibodies as well as part of the first-line therapy, whether it be as maintenance after their stem cell transplant or in some other form. Those are the trials that I really look forward to.

We are also trying to evaluate whether there is a role for trispecific antibodies where instead of targeting only say one protein, the BCMA, we could target two different proteins on the myeloma cell. So, we are working on getting a trial where a particular drug is targeting CD3 on the white cells and two proteins on the myeloma cells, which is CD38 and B-cell maturation antigens. I really look forward to that trial as well, where we could understand whether somebody who has progressed on these other FDA-approved bispecific therapies could potentially respond to a trispecific antibody. That remains to be seen.

Elissa: What benefit is that to be able to bind to two different targets on the myeloma cell? Does it help destroy it faster? How does that work?

Dr. Shah: It really depends on each individual patient. But, typically patients who are getting bispecific antibodies are patients who will lose their response to the bispecific antibodies. A particular group of those patients may lose their response because they're losing their target, the BCMA, for example, on their myeloma cell.

So, the thought is that, hey, if I have a drug that's targeting two proteins instead of one protein on the myeloma cell, maybe it's possible that these patients could still respond by having a higher or more specific binding to the myeloma cell or you could think of it like having two options rather than one for the drug to kill the myeloma cell.

Elissa: Wow, well that is just really interesting to hear about trispecific antibodies and then all these other, emerging trials.

So, our final question today, on our patient podcast homepage, 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 myeloma?

Dr. Shah: So, what I tell my patient, any patient that comes to me with multiple myeloma is that this is not a curable cancer at the moment. But we have these promising new therapies that are showing such effective responses in patients who've been through six, seven, eight different lines of therapy and are still responding to this group of agents. So, I don't think that a cure is much further away. These promising agents certainly give us a lot of hope of having a cure for multiple myeloma at some point.

Elissa: Wonderful. Well, thank you so very much, Dr. Shah, for joining us today. It was really exciting to just hear how many treatments are available for multiple myeloma to keep trying and give them that longer-term remission. So, again, we really appreciate you joining us.

Dr. Shah: Thank you, Elissa, it's my 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.

Did you know that you can get more involved with *The Bloodline* podcast? Be sure to check out our Subscriber Lounge where you can gain access to exclusive content, discuss episodes with other listeners, make suggestions for future topics, or share your story to potentially be featured as a future guest. You will also receive an email notification for each new episode. Join for free today at TheBloodline.org/SubscriberLounge.

In addition to the Lounge, we could use your feedback to help us continue to provide the engaging content for all people affected by cancer. We would like to ask you to

complete a brief survey that can be found in the show notes or at TheBloodline.org. This is your opportunity to provide feedback and suggested topics that will help so many people.

We would also like to know about you and how we can serve you better. This survey is completely anonymous, and no identifying information will be taken. However, if you would like to contact the LLS staff, please email TheBloodline@LLS.org.

We hope this podcast helped you today. Stay tuned for more information on the resources that LLS has for you or your loved ones who have been affected by cancer.

Have you or a loved one been affected by a blood cancer? LLS has many resources available to you – financial support, peer-to-peer connection, nutritional support, and more. We encourage patients and caregivers to contact our Information Specialists at 1-800-955-4572 or go to LLS.org/PatientSupport. You can find more information on multiple myeloma at LLS.org/Myeloma. All of these links will be found in the show notes or at TheBloodline.org.

Thank you again for listening. Be sure to subscribe to *The Bloodline* so you don't miss an episode. We look forward to having you join us next time.