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THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'There's Always Hope: Myelodysplastic Syndromes (MDS)

Description:

Research continues to accelerate for myelodysplastic syndromes (MDS), giving hope to patients and their loved ones. In this episode, Dr. William Shomali of Stanford University dives into cutting-edge treatments for both low and high-risk MDS. Learn about the innovative therapies that are enhancing quality of life and explore the promising strides towards curative treatments. Don't miss this inspiring conversation filled with valuable insights and hope for a brighter future.

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. William Shomali, a Clinical Assistant Professor of Hematology at Stanford University School of Medicine in Palo Alto, California. Dr. Shomali specializes in the treatment of blood cancers, such as myeloproliferative neoplasms or MPNs and myelodysplastic syndromes or MDS. He aims to provide compassionate, personalized, and evidence-based care to each patient. Welcome, Dr. Shomali.

William Shomali, MD: Thank you for inviting me.

Elissa: So, our episode today is on myelodysplastic syndromes, or MDS. Could you explain to our listeners what that is?

Dr. Shomali: Yes. So, myelodysplastic syndromes, now we call them syndromes because it's more than one subtype of disease, and to divide it, myelo comes from myeloid, which is blood-forming cells; and dysplastic is abnormal growth of these cells.

Syndromes is a concurrence of several symptoms in a disease. So, to put it all together, it's a spectrum of blood cancers where the bone marrow, blood-forming cells are abnormally looking; and that can cause low blood counts, what we call cytopenias. And this disease can progress to another disease called acute myeloid leukemia (AML).

Elissa: Okay, so it's a group of diseases then. How many different diseases are under the MDS umbrella?

Dr. Shomali: We continue to learn more and more of this disease, and now we have genetically defined subgroups according to their mutation or the chromosomal abnormality. So, they continue to learn.

Lizette: So, doctor, what are the typical signs and symptoms of MDS; and what would generally bring someone to the doctor to be evaluated?

Dr. Shomali: So, it can be like, "I'm feeling more tired, more fatigue, short of breath." I go see my primary care physician, and they do a blood count, and then I'm found to be anemic with a low hemoglobin. Or it could be that the patients can present with an infection, and either come to the hospital with that infection or an infection that's taking longer to heal, so they go and see their primary care. They check the blood counts and their neutrophils, or the subtype of white cells, is low. Or patients can present with bruising or bleeding and their platelets will be low. And in some patients, when they do their routine blood work, they notice that the hemoglobulin, the red cells or the white cells or their platelets are slowly dropping over time.

Elissa: So, can you explain primary versus secondary MDS and how that may affect treatment and prognosis?

Dr. Shomali: Yes. So, primary is what we most commonly se, where it happens usually randomly that patients acquire MDS. Whereas, secondary comes after patients received chemotherapy or additional therapy for another type of cancer. Most patients

have primary smaller percentage have secondary. And then secondary carries a high risk of disease progression.

Lizette: And can you discuss high- versus low-risk MDS and how that is determined?

Dr. Shomali: Yeah, we use several calculators to help with risk stratification. And the most recent one that we use is the IPSS-Molecular (IPPS-M), where we include the counts for the patients, include the chromosomal abnormalities, and include the molecular changes on the mutations that we detect in the genes. We put everything together, and it can tell us it's very low-risk disease, it's a spectrum from very low, to low, up to very high risk of disease.

Lizette: So, does the risk level actually determine the prognosis and the treatment?

Dr. Shomali: Yes, it affects both. Let's talk a little about the prognosis. So, it's a spectrum of disease. So, the very low-risk, the average, patients we see survival around ten years. That's the average. And whereas in very high risk, the average is around one year. The rest of my patients, those are statistics. But you are a person, you're not a statistic, so your numbers likely would be different. But that's how I will use these calculators.

And those affect how we treat. Like, for example, for very high-risk disease or high-risk disease, we would like to use transplant early on. But as in very low-risk disease or low-risk disease, we don't want to use transplant early because it also can have complications from the transplant. So, we try to delay it.

Lizette: Right. And we also know that in some cases MDS could turn into AML. Are there factors that may predict it turning into AML, and really how often does that happen?

Dr. Shomali: Yeah, also it depends on the risk stratification. So, for example, in someone who's very low-risk disease, after four years of diagnosis, less than 4%, less than 4 out of 100 patients with very low-risk disease will progress to acute myeloid

leukemia. Whereas if someone has very high-risk disease, we're talking about 40% of patients by four years will have acute myeloid leukemia. And usually, the risk is also high beginning at the first year. It reaches around 30% in very high-risk disease. So, this is where we try to use more and more transplant early on.

Lizette: Okay. Yeah, that's good to know because I know that some patients think that it'll automatically turn into AML, and that's not the case.

Dr. Shomali: That's true.

Elissa: And I'm sure patients are listening that may be in the higher-risk category, and it has not turned into AML yet. But they might be wondering if it does turn into AML, would they be able to stay with the same treatment team since you specialize in MDS? Would you also be continuing to treat them for AML?

Dr. Shomali: Yeah, that's an important question. It depends on the institution, so it's institution-specific. But many times, we continue to follow like the same physician. We continue to follow the patient. We are now more and more subspecialized in our institution, so you will see physicians will treat only MDS, physicians will treat only AML. So many times, you will see there might be some transition, especially if there's a clinical trial available.

Elissa: Okay, I'm sure that's something that patients will think about because we tend to get very connected with our oncologists; and so it might be a little difficult if we're thinking that we might have to move to somebody else. So, thank you for answering that.

So, let's talk about treatment. What are the current treatments for MDS?

Dr. Shomali: So, when I think about treatment of MDS, I think about the risk score. Is the patient on the lower-risk score or on the higher-risk score, and is the patient symptomatic or not? So, if the patient has lower-risk disease and the counts are slightly low, we call it mild cytopenias. But the patient is not symptomatic from those,

we don't need to treat. We just observe. We monitor the blood counts and see the patient. Make sure they are feeling well and they're not having new symptoms.

Whereas, for example, if they are lower-risk disease and the hemoglobin's dropping, and they are becoming symptomatic from it, like they tell me, "I'm feeling more tired. I need to take naps during the day. I'm not able to do what I like to do," so we try to improve the hemoglobin. This is where we have several agents that we can use. One of them is a hormone, like we call them erythropoietin-stimulating agents. We all have a hormone called EPO that our kidneys produce; and we learned if we give extra of this hormone, our bone marrow will produce more red cells. So, we can use erythropoietin in some patients.

We can use another agent called luspatercept, which was recently approved for MDS. Erythropoietin acts early on to stimulate the production of more red cells. Luspatercept acts later, let's these red cells to mature because in many times in MDS because of inflammation that's going on, these red cells, like they grow in the marrow, they die in the marrow without maturing. So, luspatercept can help with the maturation.

If we find an abnormality with chromosome 5, 5q syndrome we call it, we can use a pill called lenalidomide. Most recently we have another IV infusion approved called imetelstat that we can use also for the anemia. And if we try multiple agents and nothing works, we can go to hypomethylating therapy at that time like azacitidine or decitabine or there is the oral decitabine form.

Elissa: Okay, so what happens then with higher-risk patients?

Dr. Shomali: Yes. So, we talked about lower risk without symptoms, lower risk with anemia. There's the patients who present with lower risk with low platelets, thrombocytopenia. In those patients we can try what we call thrombopoietin receptor agonists. These are platelet boosters. There is a subcutaneous form, and there is an oral form. The subcutaneous called NPlate®, the oral form called eltrombopag. So, we

can try a dose; and if it's not working, or there's a contraindication to dose, we can use also hypomethylating agent like azacitidine or decitabine. If the patient has lower risk and the main symptoms are recurrent infections because of their low neutrophils, low white cells, we can use white cell boosters like filgrastim or Neupogen®. And also, if we see the patient is anemic and , there's low platelets and low white cells all together and we want to improve the counts, we can use the hypomethylating therapy from the get-go to improve multiple counts at the same time.

If the patient has high-risk disease, we want to aim to improve the natural history here. It's not only improving the counts and improving their symptoms, but we want to delay the progression to acute myeloid leukemia and try to have the patients live longer too.

So, here we use hypomethylating therapies and sometimes we add a pill called venetoclax, depending on the blast percentage that we see in the bone marrow.

Elissa: Okay, so for low-risk disease, really we're looking at more managing symptoms and quality of life versus finding potentially curative treatments?

Dr. Shomali: Yeah, because we always have to balance the risk of side effects with the risk of the disease itself. If I want to take a medication that will cause more side effects than the disease, I would ask myself am I doing the right thing? So, lower-risk disease, we know that the treatment that we currently have, the hypomethylating therapy or the bone marrow transplant has high risk of complications compared to the disease itself. Whereas, in the high-risk disease, we know the disease will progress, and the disease will cause complications. So, we say, okay, now we want to take a little bit more intense treatment because we want to change the course of their disease. And I forgot to mention in the high-risk disease that bone marrow transplant is the way we can cure this disease.

Elissa: Okay. And we've also heard a lot about CAR T-cell therapy and bispecific antibodies. Could you explain what those are, and are they currently available for MDS?

Dr. Shomali: This is an important question that patients ask often in the clinic. So, CAR T therapy is chimeric antigen receptor T-cell therapy. And bispecific is a type of immunotherapy where we ask the immune cells to come and attack the cancer cells. So, in CAR T, we are still in MDS lagging behind on what we can do in lymphoma and in acute lymphoblastic leukemia. That, part of it because to have a target to attack on the leukemia cells on the MDS cells without affecting the normal cells has been difficult.

So, there are trials in CAR T attacking a marker called CD123, but it's early.

So, the way the CAR T works, we take T cells from the patient, activate them in the lab by inserting a receptor to those T cells, and then infuse them back to the patient. They go inside the body of the patient, and they go try to attack the cancer cells. And that hopefully helps to control the disease. But sometimes also, it can cause what we call cytokine release syndrome (CRS) where it cause all the inflammation when that happens because we're activating the immune system at once.

Now, with the bispecifics, we're not taking cells from the patient and activating them outside of the lab. Here, we're giving a medication, we call it bispecific because it can bring the T cells, usually T cells with a CD3 as the antenna on the T cells. And we're looking at a marker on the myeloid cells. One of them is CD123. The one we talked about in CAR T. So, you bring these T cells which has CD3 next to the CD123, and so they bring them together so the T cells can attack the former cells. Still, we have early studies in that, and we're learning more and more about that in MDS and AML.

Elissa: Okay, so currently really the only curative treatment right now is a bone marrow transplant?

Dr. Shomali: Correct.

Lizette: And for those folks that aren't eligible for bone marrow transplants because don't you have to be eligible for a bone marrow transplant at this point? How do you decipher who is eligible for a bone marrow or a stem cell transplant?

Dr. Shomali: Thank you. This is very important question, so there are multiple factors that play a role when we talk about eligibility for a bone marrow transplant. Age by itself is not a contraindication. So many patients when they hear like for someone who's above the age of 65, 67, 68, they think, oh, we're not eligible. No, it's that we do it to 75-, 76-year-old patients. So, age by itself, it's most important as the functional status.

Lizette: Yeah, you're right. A lot of our patients are asking because this disease, in general most patients are in advanced age, right?

Dr. Shomali: That's correct. Yes, the average age of patients are in their 70s when they are diagnosed with this disease.

Lizette: Wow, and I know that you started mentioning side effects, so what are the side effects that many patients will have from treatment and really are these side effects manageable?

Dr. Shomali: Yes, yes. So, we work together with the patients so they can report if they have side effects; and we try to minimize them as much as possible.

When someone has lower-risk disease and we're using erythropoietin-stimulating agents, those usually are well-tolerated. It's a subcutaneous injections, similar to someone who injects insulin, for example, but might have some local reaction when they have their injection. Some pain at this site, inflammation on this site. We monitor their blood pressure with the erythropoietin-stimulating agents because their blood pressure can go up with these medications.

When we use, for example, luspatercept, similar side effects as we can see, local injection site reactions. Their blood pressure we will need to monitor and monitor for headaches, and fatigue has been noticed to be more common with luspatercept compared to erythropoietin-stimulating agents, so it matters for that. So, for some patients, we see the hemoglobulin improving, but they are having fatigue, for example. So, we have to decide is the fatigue from the hemoglobulin or from the treatment itself.

Lizette: Oh.

Dr. Shomali: With lenalidomide, the pill, we monitor the blood counts because it can cause the white cells the platelets to go down, so want to keep an eye on those. In addition, it can cause, increase the risk of blood clots. So, if someone is taking lenalidomide, we try to make sure they are taking baby aspirin, for example, if there is no contraindication to prevent the risk of blood clots.

Imetelstat, the most recently approved medication where you need to monitor their blood counts because the platelets can drop, and the white cells, so we need to keep an eye on that, keep an eye on the liver function test.

With hypomethylating therapy, at the beginning, especially at the first couple months of treatment, we can see the significant total cytopenia, significantly low blood counts where that can increase the risk of infection, increase the risk of bleeding. Patients can need blood transfusions more often during that period because these medications, at the beginning, we are killing the bad cells in addition to the good cells. So, we're waiting for the good cells to come back at the end of each cycle. So, during that period, we're more prone to these side effects.

And it takes about two cycles to see the response. So, I tell my patients usually the first one to two cycles are the toughest for their treatment, and then it becomes easier with the hypomethylating therapy.

Lizette: Can patients be on transfusions for a long period of time?

Dr. Shomali: Yes, yes. Transfusion support is key because when patients are first diagnosed, many of them are diagnosed with very low hemoglobin, and they need transfusion. And they would get their diagnosis, continue with transfusion support. And when we start treatment, we continue transfusion support till we see a response.

So, what happens if someone is taking a lot of transfusions, like more than 20 units of blood, iron can build up. It can build up in the liver, it can build up in the heart. So, at that time, we start thinking maybe we need to consider what we call iron chelation. It's using a medication to lower the iron in the body so it can let, cause less and less complications.

So, iron chelation, we have several agents that we can use there. There are pills and there's subcutaneous IV formulation. We usually, iron chelation, we wait till the iron levels go up. Many times, we follow a marker of the iron called ferritin. There's no agreement which ferritin level that we should start iron for it. But we also count how many transfusions that the patient, and we also think about what is the risk of their disease. So, if we know this is a lower-risk disease and the patient needing transfusion, and we know this will be long-term treatment, we think of iron chelation because iron chelation would help decrease the iron, but this is slow to work. We need to give it time to work, so it needs three to six months to see the effect of iron chelation.

We monitor iron chelation with the possible side effects also. We do a hearing exam. We monitor the liver enzymes, the kidney enzymes to keep an eye on those during iron chelation.

It's important to learn that these are slow to work. It's not like I start iron chelation today and tomorrow my iron levels will go down. It takes much longer.

Lizette: Yes, and also what you mentioned, fatigue with a lot of patients, is that it also takes time to feel like patients can get up out of bed again. I know a lot of patients that have extreme fatigue.

Dr. Shomali: Yes, yes. The nice thing about blood transfusions, they work very quickly. So, the patients get them today, and tomorrow they tell me "I feel better, I am able to function and do what I like to do."

The other medications might take longer to see the effect, see the improvement in the hemoglobin. Usually when the hemoglobin is above 10 where patients feel they have enough energy to do what they like to do. Usually, we see the fatigue more when the hemoglobin's below 10 in children. Then, we save the transfusion for someone with hemoglobin less than 8 or less than 7 because transfusions can have build iron, so we try to save them to that level.

Elissa: Okay, now you've gone over quite a lot of side effects. I know a lot of patients think about potential of late term or very severe side effects. Is that possible with any of the treatments?

Dr. Shomali: This is important question. When you say late-term side effects, like, patients worry about development of secondary malignancy, for example, another cancer from the treatment. So, the treatments we discussed like in lower-risk disease, I'm not aware of a study that shows that dose can increase this cancer.

That being said, if the erythropoietin-stimulating agents, if a patient has concurrent cancer, like someone has MDS and concurrent, for example, in breast cancer, we don't like to give erythropoietin-stimulating agents because what we, in these other solid tumors we call them, like breast cancer or prostate cancer, they can have receptors on them for EPO, for erythropoietin. So, what we worry about that we're treating the MDS, but we worry that maybe the breast cancer would go with those.

So, it sort of becomes a discussion with their patients about the quality of life, right? So, if the patient tells me, "I know it might increase the risk of their breast cancer progressing, but I'm taking treatment for it. I'm being monitored for it, and I don't want to get any transfusions. I'm okay taking this risk." Other patients tell me, "No, I prefer to take transfusions. I don't want my breast cancer, for example, to have the possibility of growth." So, it depends on each patient.

Elissa: And any really serious side effects that patients need to be aware of that are a potential?

Dr. Shomali: Yeah, I tell my patients when we start especially the hypomethylating therapies, any fever, they need to come in because when they get a fever, the immune system is down, and they will need blood cultures and antibiotics through the IV. So, if it happens on a Friday evening, don't say, "Okay, Monday's coming. I'll wait till Monday and see my physician on Monday." No. Please, you need to come to the emergency room if you have neutropenic fever. When we say neutropenic fever, I worry that it can progress to a severe infection, so we need to act early on it.

Elissa: Yes, absolutely. As an AML survivor, I know that neutropenic fevers can progress very, very quickly. So, you need to get seen very quickly. That is good to let them know about that.

So, let's move on and discuss emerging therapies. Are there any new therapies or those on the horizon that you're particularly excited about?

Dr. Shomali: Yes. So, we had the recent Annual [American] Society of Hematology (ASH) meeting. So, I can provide risk certification updates, in lower-risk disease and updates in higher-risk disease. So, there was a new study from Europe trying to assess patients with a 5q abnormality because many of these patients are like, maybe respond, but their response is shorter than we like and they progress. And I always ask myself like what risk factors are causing this higher chance of progression?

So, what we learned is that if someone presents with low blood, low platelet counts, if someone has a mutation in SF3B1 with the 5q, this might be a high risk of progression. This is where we have closer monitoring and also doing transplant earlier, for example.

When we see SF3B1 mutation, in general, we think of it as a favorable mutation to have. That it's associated with lower risk of disease progression over time. But if it happens with 5q, for example, it's not a good combination. And we have to think, maybe this is a high-risk disease we need to monitor more closely.

In the lower-risk disease, there is now more studies to study the combination of these agents we discussed. So, we talked about erythropoietin-stimulating agents. We talked about luspatercept. So, there are now studies trying to combine both to see if we can make them all produce more cells. And they move the breaks for the maturation; can we have better response and higher chances of response? So, those are ongoing.

In the higher-risk disease, there was a study from China that shows the importance of doing Phase III trials, which is like comparing the standard of care to the new study drug. So, they compared the hypomethylating therapy decitabine to using decitabine plus a special form of vitamin A called ATRA (All-trans retinoic acid). This is a special one that we use in another disease in AML called acute promyelocytic leukemia. It's very effective in APL. We wanted to learn more about it in MDS.

So, when they compared it both together, using decitabine alone versus adding ATRA to decitabine, they noted maybe there are higher response rates when we add ATRA. But, unfortunately, it did not translate that patients who took that ATRA lived longer. So, that's what makes it very important to do these trials, so we don't give treatments that don't show that they are improving also the survival of patients. Because if we used only depending on the single agent like the single Phase II trial, for example, where we used decitabine-ATRA without a control arm, we will say, "Oh, there's a higher response rate than what we see usually. So, let's use it for everyone." But if

you do randomized trial, and it tells you, if you do this, patients are not living longer; then, no, we should not be doing this. Maybe we need to try another combination.

Elissa: Is there anything emerging that might be able to prevent those really high-risk patients from turning into AML?

Dr. Shomali: Yes. So, we've talked earlier about when we use hypomethylating therapy, sometimes we add a pill called venetoclax, a BCL2 inhibitor. There is a trial ongoing, comparing azacitidine as a single agent versus azacitidine plus venetoclax. So, we're waiting on the results of this trial to see if patients would take the combo, how high the response is, but not only higher responses. We want to see also patients living longer when they take this combination.

Elissa: Great. Well, hopefully, by the time we get around to our next MDS podcast, we'll have some results of that. So, that's exciting.

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 MDS?

Dr. Shomali: Yeah, there is always hope. The field is changing rapidly, and every day we learn new things and I advise my patients if there's a clinical trial, either way they have to consider this because we want to always help the patients and advance the treatment in this disease too. So, it's clinical trials that give hope. And now, when we try clinical trials in high-risk disease and, of course, using it early on we compare to the standard of care. So, everyone, we're getting the standard of care and then on top of it trying a novel agent to see if that helps.

Elissa: Yes, clinical trials are definitely so important to move forward research and also give patients that opportunity to try a new drug that might work really well for them.

And we will have information in the show notes for listeners if you'd like to look into clinical trials. We have our Clinical Trial Support Center that can get you matched with one.

Thank you so much, Dr. Shomali, for joining us today and telling us all about MDS, the different types and risk stratification, and all the emerging treatments that are coming out. We're excited to see where that goes and see if we can continue to get out these great treatments and also look into these immunotherapies as well and see if we can get those working for MDS. So, thank you again so very much for joining us today.

Dr. Shomali: It is my pleasure and thank you for inviting me.

Elissa: Thank you.

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