LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Instilling Hope Through Progress: Myelodysplastic Syndromes (MDS)'

Description:

Join us as we speak to Dr. Anand Patel and Dr. Satyajit Kosuri from The University of Chicago Medicine about the latest treatment advances for myelodysplastic syndromes (MDS).

In honor of MDS Awareness Day on October 25th the doctors discuss how MDS develops, why genetic mutations matter when choosing a treatment course, and how stem cell transplantation, targeted treatments and cellular therapies bring hope to more MDS patients and their families.

Transcript:

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

Jesse: I'm Jesse.

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

Elissa: Today we will be speaking to Drs. Anand Patel and Satyajit (Satya) Kosuri about myelodysplastic syndromes, or MDS, in honor of MDS Awareness Day on October 25th.

Dr. Patel is a hematologist/oncologist at The University of Chicago Medicine who specializes in the treatment of myelodysplastic syndromes, myeloproliferative diseases, or MPNs, and leukemia. In addition to treating his patients with standard treatment approaches, he is committed to delivering novel therapies through clinical trials that combine basic and translational research into groundbreaking advancements in medicine for better outcomes and quality of life.

Dr. Kosuri is a Medical Oncologist and Clinical Director of the Hematopoietic Cellular Therapy Program at the University of Chicago Medicine. He treats adult patients with acute leukemia, myelodysplastic syndromes, myelofibrosis, and multiple myeloma. He is experienced in stem cell transplantation with clinical research interest in improving patient access to transplant and preventing and treating graft-versus-host disease, or GVHD. He is passionate about guiding his patients through the treatment process and working with a multidisciplinary team of physicians to provide state-of-the-art care.

You may recognize Dr. Kosuri from when he joined us on a previous podcast titled "Transplant Support in Graft-Versus-Host Disease," in December of 2021.

Welcome Dr. Patel and welcome back Dr. Kosuri.

Anand Patel, MD: Thanks so much for having me.

Satyajit Kosuri, MD: Thank you for having us. Really appreciate it, and we're looking forward to it.

Elissa: Great. Well, our topic today is on myelodysplastic syndromes, or MDS. Could you tell our listeners what that is?

Dr. Patel: Yeah. So, myelodysplastic syndromes, or MDS, broadly speaking, it's a blood cancer. It's a cancer of the white blood cells and can impact our platelets, which are our clotting blood cells; our red blood cells, which carry oxygen to the parts of the body that need it; and then with it being a disorder of white blood cells, it can also have impact on our ability to fight infections.

Dr. Kosuri: Yeah. I sit down in front of patients and family members in the clinic, one of the things that I let them know is that this falls into a category, as Anand's alluding to with the low blood counts, what we call bone marrow failure syndromes. And I make an analogy for the patients that, "Don't forget that the bone marrow is an organ just like your heart's an organ, your liver is an organ, your kidneys, your lungs, etc., and that, just like those organs can fail, bone marrows can fail as well." So, you

get these bone marrow failure syndromes, you end up getting low blood counts. And I often will tell them that it's like the factory in your body, that makes all the cells of your blood system, but also make the cells that end up becoming a, hopefully, healthy immune system and so two very important components that make a human being functional.

And if there are some sort of disturbances within the factory, it's not able to put out the products, like Dr. Patel is mentioning, of the white blood cells, the red blood cells, and the platelets, and you end up running into a lot of problems. So that's how I explain MDS to patients and their family members when they come see me in clinic.

Elissa: Now, when you're talking about disturbances in the factory, are you talking about gene mutations?

Dr. Kosuri: Yeah. So there are many disturbances that can occur. As we think of these blood cancers and these bone marrow failure syndromes, we think about things like age. Age is a major risk factor. We know that patients with MDS are in the age group in the 60s and 70s, and we know as we age the human body develops mutations. And under normal circumstances, the immune system is able to look for these cells that have these mutations and are acting out and is able to eradicate them.

However, with time, we also know that the immune system of patients in these age groups is not as optimal. So, let's say you have a mutation that you pick up with age in your 70s, and you have some cells that are not behaving as they should. Well, you also may have an immune system that is not working as optimally as it was back when this person was in their 40s or 50s and able to eradicate these cells.

And then you get this accumulation of these cells that are not regular and then they start to develop various issues, one of which can be MDS. And this can also lead to other issues or other cancers that can be involved. But the gene mutations are one of many causes that can lead to a disease such as myelodysplastic syndromes.

Dr. Patel: Yeah. And to jump off what Satya just said, in addition to mutations and specific genes, sometimes we'll find that there are what we call chromosomal abnormalities. So, chromosomes harbor where all of our genetic materials is, where it's packaged up; and if there are extra pieces of chromosomes or pieces that are missing, that can also be something that then leads to the development of MDS. So, looking under the broad umbrella of genetic abnormalities that would encompass chromosomes that are either missing or if they're extra chromosomes, mutations in specific genes as Satya had mentioned.

And the other thing we know when it comes to MDS is not all chromosomal abnormalities and genetic mutations are the same. Many times, which chromosomal abnormalities or genetic mutations are present can allow us to get a sense of the pace of MDS in someone whether it's something that can be monitored closely or whether it's something that needs treatment sooner rather than later. These are some of the additional information that we really need to be able to sit down and have a discussion about what the best approach is moving forward if and when someone is diagnosed with MDS.

Lizette: Sure, and Dr. Patel, also one thing that is unique about MDS is that it's really a group of diseases, right? Can you tell us more about that and how it differs from other blood cancers?

Dr. Patel: Yeah, absolutely. You're 100% right. Myelodysplastic syndromes encompass a spectrum of diseases and really what you can see when talking to patients, sitting down with them and reviewing their clinical history, their lab work, is the different flavors that MDS can have.

So, for some patients, the most predominant thing we see is issues with low blood counts, and that can be the white blood cells, the platelets, and/or the red blood cells. So many times, for those patients, we need to figure out how to overcome the fact

that the factory isn't working well. And sometimes it means giving it some extra stimulation to create those appropriate blood cells.

Other times, MDS can manifest with an excess of immature cells called blasts, and it may be behaving more like an acute leukemia. In that situation, we may talk about and think about what are strategies to help reduce or eradicate those immature cells or blasts that are in the bone marrow to allow the factory to start functioning normally.

In addition, when thinking about the umbrella of MDS, how someone may have developed MDS can kind of color how we think about it as well. So, for many patients, if and when they were to develop MDS, there may not be a specific thing that we can point to that may have caused the MDS to develop, so it comes anew or de novo.

On the other hand, there's a broad bucket of what we call secondary MDS, which is when we have a specific reason or a fairly certain reason that we can point to that was a risk factor in the development of MDS. Some examples of that could be being treated previously for a cancer with chemotherapy or radiation therapy can predispose someone to developing MDS. Having a different bone marrow failure syndrome, such as aplastic anemia, which with time progresses to something like MDS; or being born with a mutation in your genes that predisposes someone to the development of MDS, what we call a germline syndrome.

Jesse: Dr. Patel, we know that MDS can evolve into acute myeloid leukemia, or AML. Does it always evolve into AML?

Dr. Patel: The risk of that happening varies from patient to patient, and we use some of these characteristics that we were talking about earlier; the blood counts, the blast counts, genetic mutations, chromosomal abnormalities, to try and get a sense of what is the risk of progression to AML. For some patients, that risk is very low. It can be truly decades before there'd be any significant risk or chance of the disease evolving to AML.

For other patients, their MDS may be behaving very much so like AML from the get-go and there's a high risk of progression. But being able to use these tools that we have and what we call prognostic systems helps us refine and understand what the risk is of MDS evolving to AML.

Dr. Kosuri: Anand, can you expand on that prognostic scoring system that you use when you see a patient? How do you go about it and how do you communicate that to patients?

Dr. Patel: Of course. The first thing I want to emphasize is prognostic scoring systems are a tool but they by no means tell the full story when you're trying to get a sense of how to best manage a diagnosis of MDS and counsel a patient about their diagnosis of MDS.

So prognostic scores, in general, are developed by looking back at hundreds, and sometimes thousands, of patients who have had a specific disease, MDS in this case, and then tracking what the outcomes were of those patients over time and determining what factors may have led to better outcomes and what factors may have led to more high-risk things happening, like the development of leukemia.

For many years, we've been using a scoring system called the IPSS, and that scoring system has been refined over time. The IPSS-R incorporated chromosomal abnormalities. And very recently, actually earlier this year, we now have a prognostic system called the IPSS-M that also incorporates genetic mutations. So, when talking about that with a patient, I can't emphasize enough that that may give us a broad sense of what's going on, but, again, we are kind of pulling and interpreting data from hundreds of people and then trying to apply it to the person in front of us. And there's always some degree of imperfection that comes with that.

Dr. Kosuri: One thing I wanted to add is, as Anand's mentioning, another important aspect is the behavior of their underlying disease. So, you can get a specific score from these prognostic tools, but it does not tell the entire picture. Someone may be

on the lower-risk category, but if you see that over time their disease is behaving in a different way, maybe it's not involving just their white cells, now it starts to involve their red blood cells or now they're starting to exhibit low platelets, we understand even in spite of the prognostication that was done at the time of their diagnosis that it's an evolving picture. It's an evolving disease. So that's something that the MDS physician will take into account and talk to their patients and their family members about.

Elissa: Oh, that's really interesting. Speaking of genetic mutations and testing, last year we interviewed one of your colleagues, Dr. Lucy Godley, and her patient Ashley, on hereditary MDS. Ashley and her brother were both diagnosed with MDS a few years apart. Her brother ended up turning into AML and passing away, and Ashley had a stem cell transplant, which required some additional genetic testing for her donor. Would you tell us a little more about the likelihood of family members both having MDS and what that could mean for transplant or treatment?

Dr. Patel: I can certainly comment on the genetic aspect of MDS, and then I'd love for Satya to weigh in about how that may impact decision-making around transplant.

First of all, work done by Dr. Godley and other experts in looking at hereditary syndromes that predispose patients to the development of MDS has really taken over the last decade or so. We know so much more now than we did even 10 years ago. And, broadly speaking, it seems that somewhere in the neighborhood of 10 to 15% of patients with MDS have a hereditary or a germline syndrome that may have predisposed them to the development of MDS.

Now for select patients, the curative option that may be discussed in pursuit is receiving an allogeneic stem cell transplant. Many time, we think about whether family members or siblings are potential donors, and that's why the hereditary component of disease can potentially matter. Satya, I'd love for you to chime in.

Dr. Kosuri: Sure. So, when you were saying Ashley's name, I was smiling from ear to ear because I transplanted Ashley over-

Elissa: Oh!

Dr. Kosuri: -five years ago now. I think she just had her five-year anniversary.

Elissa: Yes.

Dr. Kosuri: She loves to do social media something called the Boomerang or something. Every year we do one of these Boomerangs and she puts it up somewhere. I'm glad that you brought that up. It's a really nice story, and it's important to bring up now because in the field of transplantation, this is something that we are paying more and more attention to.

When we think about transplant and we think about these potentially inherited disorders, it's very important to us because I will use Ashley's example as it has already been in another podcast. But as you said, both her brother and her had the same germline mutation, which is called a GATA2 mutation and as Anand was mentioning, there are specific mutations that can be familial that can predispose people to develop various blood cancers or bone marrow failure syndromes. In Ashley's case, her and her brother had the actual physical manifestation of this mutation although other people in her family did not have blood cancer.

That's where it can be a little bit tricky. As we gain more and more information about these inherited predisposition syndromes, when it comes to transplant, there is a hierarchy of what we would want as a donor. So, the first option A for donation is looking for a fully matched sibling donor. If we don't have a fully matched sibling donor, and about 30% of patients who need an allotransplant do so the majority do not, then we go and look at matched unrelated donors. And then the third option in many cases can be what we call alternative donors, which are half matched donors or cord blood.

When we consider someone, a brother or sister, for evaluation for an allogeneic transplant understanding that there may be a familial predisposition mutation in the family, even though it has not manifested physically in that brother or sister, is important because that makes us want to know does that brother or sister harbor a mutation which if we collect the stem cells from that person, the way we collect the stem cells can be affected.

And then number two, if we give these stem cells from the brother or sister to the recipient of the transplant, what are the implications down the road? Will they develop what we call a donor-derived malignancy, a donor-derived leukemia down the road? So, you kind of get back to square one. And that's something that we want to avoid.

When we think about familial predisposition in regards to transplant, it's important from a donor workup perspective and it's important from a timing perspective because we want to get people to transplant as quickly as possible. And these genetic workups are not something that can be done extremely quickly. So, it takes a little bit of time. And if the patient's acute leukemia or other disease is not allowing us a significant amount of time, we have a window of opportunity, this comes into the transplant physician's calculus about whether or not I should just go ahead and look for a matched unrelated donor or some other alternative.

So that's very important, and it's a very good question, and Ashley's example is really the textbook example of how these mutations, as we learn more and more about them, can affect the way we come into transplant and how quickly we need to move in regards to nailing down a donor.

Jesse: To further the discussion about treatment, what are the current standard of treatment options for MDS?

Dr. Patel: Yeah. It's a field that's under rapid evolution I would say. It helps to think about how is the MDS impacting a patient's blood counts and what we're seeing on their bone marrow.

In patients who have MDS where predominantly the impact is on one specific type of blood count, and let's take the red blood cells as an example, there are therapies that can be used to very specifically target that and try to improve those blood counts. For example, sometimes erythropoietin, which is the hormone that stimulates the bone marrow to make red blood cells, we can administer injections of that to patients to try and overcome the fact that the MDS is not allowing for appropriate production of red blood cells.

In some patients with anemia or low red blood cells related to MDS that have a specific genetic abnormality, called an SF3B1 mutation and have a type of MDS called ring sideroblasts, sometimes we can use an injection called luspatercept to help overcome that. As someone's MDS involves more types of blood counts or if we find that those initial strategies are not working, we have to then think about therapies that may be broader in their ability to impact the MDS cells.

For the last 20 years or so, one of the mainstays has been a family of medicines called hypomethylating agents, or HMAs for short. And currently, there's a medicine called azacitidine, which can be an injection or an IV. There's a second medicine called decitabine, which can be given as an IV. And within the last year or so, there's been FDA approval for an oral version of decitabine combined with a second drug called cedazuridine, which allows for you to take the decitabine as a pill, not have it get broken down in the stomach.

The HMAs, I would say, form the backbone of therapy in higher-risk MDS or MDS that may be lower risk but the initial kind of attempts to improve blood counts have not been as effective as we would want.

There's also much work being done to see how we can improve upon the backbone of HMAs. So, there are a number of what we call Phase III trials, meaning trials looking at very promising drugs and hoping to confirm the benefit of those drugs compared to our current standard of care. And I'll highlight just a handful of drugs. Right now,

there's an oral pill called venetoclax that's being looked at in combination with azacitidine, there's an IV antibody called magrolimab that's being looked at, and there's another IV antibody called sabatolimab, which is being looked at all in the Phase III setting, along with a number of other agents.

The other thing I'll add is in this day and age when it comes to curing MDS, we still do not think that these therapies have the ability to definitely cure MDS. These are therapies that, if effective, we tend to continue for as long as they're effective, and many times we can see them be effective for a prolonged period of time. But in thinking of how to definitively cure MDS, really the conversation comes back to thinking about discussing and being thoughtful around transplant.

Dr. Kosuri: Yeah. I think that's a really important point, Anand. I see patients with MDS and AML and Anand see those patients, and we have a group that works very closely together. Whenever Anand may see a patient and he has followed them, he has treated them and understands that based on the characteristics of their disease that a stem cell transplant is something that needs to be discussed with that patient, he'll refer them over to me or one of the other transplant physicians and then we work as a team to set up a treatment plan for the patient with MDS and see if they're a candidate.

One of the things Anand mentioned before and spoke in detail about is the risk stratification that we use for patients with MDS. If we see patients with this diagnosis, we use various tools like the revised IPSS score. We look at the behavior of their disease. I'll make a generalization here just for the listeners and their family members to understand that there's a lot of nuances that goes into this decision-making; but if you see patients in that intermediate, high-risk, and very high-risk groups, the conversation for transplant is something that needs to be discussed. So oftentimes these patients will get referred to me for a transplant evaluation.

I want the listeners to conceptualize the transplant candidacy as being a chair with four legs. And in order for that chair to keep you upright, all four legs need to be there, or it just doesn't work. This is how I describe the transplant candidacy process is that the first leg of the chair is really the indication for the transplant, the diagnosis and the risk stratification that Anand and I may see in a patient.

Number two, one thing that's really important when we talk about long-term outcomes is all the medications and the approaches that Anand just mentioned, are we able to use those to get the patient into a very good disease status or a remission? Because it just makes sense that the less burden of disease a patient has going into a transplant, the higher the chance of success of the transplant being able to control the disease long term.

I'll just use a random example that doesn't happen often, if someone comes into transplant with a significant blast count, Anand was mentioning the blasts for those leukemic cells, the likelihood that the transplant will keep that disease in control is less. Disease status going into transplant is important, so that makes up that first leg.

The second leg is what we were talking about as Elissa was just mentioning in the previous example, donor. Even if someone doesn't have a matched sibling, we can still get people to transplant. Compared to 15, 20 years ago, the donor availability options, our ability to transplant patients with alternative donors has grown. So, donor is less of an issue today than it was 15, 20 years ago.

The other thing that we have been talking about in regards to MDS is that the majority of the patients that are diagnosed with myelodysplastic syndromes are patients in their 60s and their 70s. And so patient fitness is an important aspect of transplant candidacy evaluation. How fit are their lungs? How fit is their heart? How active are they? What's their nutritional status? Are they able to partake in the activities of daily living?

And then I'll ask Anand, for example, "Hey, this patient went through a therapy with a hypomethylating agent or a combination of medications on or off a clinical trial. How did they tolerate that?" That is a test in itself. Did they get through that okay, or was it really, really difficult? Did they have multiple infections, multiple hospitalizations? These things will go into the calculus of understanding whether or not a patient has the physical reserve to undergo a stem cell transplant and deal with some of the pitfalls that may come along inherently with that procedure.

And then the last leg of the chair is something that may be overlooked from time to time but is just as important as the other three. And that is social support. Do they have a good caregiver or plan in place, and it doesn't have to be one person. It can be a team of people, but we need people to be around that person 24/7 for at least three months, four months and that's if everything's going well.

And also, the patient, and this the requirement with most transplant centers, is that for that first 100 days after the transplant, we require patients to be very close to our hospital if we transplant them. If things happen at home, if they get sick, they can be brought to clinic very quickly. Or if they need to be admitted, they can be admitted to our hospital where we have experience taking care of the transplant patients, that we know the patient well. It gets a little bit tricky and a little bit difficult when we have to transfer patients from other hospitals.

One thing that's important to note, and every transplant physician will tell their patient this, if it's something where you're feeling a little bit off or you're feeling sick and you feel you need to come see us, then that's fine. You can get in a car with your caregiver and come down to the clinic. Obviously, if it's anything acute, chest pain, stroke-type symptoms, or just someone is not feeling well at all, that's a 911 call: and that's going to the nearest emergency room. And then the transplant team will always work with the outside hospital to try to get them back.

So, transplant candidacy is a very detailed, nuanced discussion, as Anand is alluding to. And in regards to what is the definitive therapy for MDS, as he mentioned, we are always wanting to try to get certain patients to transplant if we can.

Lizette: Dr. Kosuri, are transplants utilized more now because I remember about 12, 14 years ago transplant for MDS was not as prevalent. I remember talking to MDS patients, and even their insurance companies weren't covering transplants for MDS back then.

Dr. Kosuri: Right. Anand made a very good point before, which is MDS and the treatment for MDS is a rapidly evolving area. And not only in the up-front therapy for MDS, but also in regards to how to include stem cell transplant within the treatment paradigm of this disease.

So, one of the things that we've been talking about is the diagnostics to, which we use in these myeloid diseases, has improved or has just naturally evolved, even in the last 5 to 7 years significantly from where we had it 15 years ago, 20 years ago.

What we are understanding as we see and as we are able to detect more mutations, or we understand that something puts someone's MDS into a higher risk category, we didn't have that information before, potentially, 15, 20 years ago. And we're able to see now and study over time if someone has a certain mutation, how does that affect the behavior of their MDS? Over this period of time, we've seen these MDS patients with these mutations or this behavior are harder to get into remission or are harder to keep in remission long term. We have to send them over to get a stem cell transplant.

So, the diagnostics have evolved. We have information and data about how the disease behaves with certain diagnostic evolution that we have. Now we're able to say this group of patients, probably more than in the past, we know how they're going to behave. We know that they may evolve into acute myeloid leukemia. And it's better to head them off at the pass rather than wait for that to happen.

And so, we're able to bring them into transplant and number one, have an indication for transplant. Number two, work more quickly than in previous decade or so to get them to transplant. So, I would agree with you that we are seeing more patients utilize allogeneic transplant for MDS; and just in general, as they often get teamed together, AML and MDS are the diagnoses for which allogeneic stem cell transplant is most utilized.

Dr. Patel: Another big factor is, over the last 15 years or so we are increasingly aware of the fact that age itself should not be a preclusion to transplant. Satya had mentioned patient fitness performance status, other medical conditions, those are certainly taken into consideration around transplant. But for patients above the age of 60 that are very healthy, otherwise fit, and transplant is considered to be the appropriate option for their diagnosis of MDS, I would say it's certainly increasingly considered and utilized now than it was 15 years ago.

At our center, the University of Chicago, we actually have a dedicated clinic called the Transplant Optimization Program, or TOP clinic where patients over the age of 60 are comprehensively evaluated as they're being worked up for a transplant to make sure that anything that can be intervened upon to make sure that that transplant is as low risk a procedure as possible is intervened upon.

So, centers are increasingly being very thoughtful about how to make sure that our patients that are being considered for transplant are being looked at in a very comprehensive way.

Dr. Kosuri: That's an excellent point. About 15, 20 years ago you would see that if you were over the age of 50, transplant was not in your future, even if transplant could potentially help that patient.

Then over time, we saw with better supportive care that we were able to go from the age of 50 to the age of 60. And now we can transplant folks in their mid-70s, late-70s even. As long as they're good candidates otherwise.

Anand mentioned the Transplant Optimization Program at the University of Chicago, which is something that we do for all patients undergoing an allogeneic transplant over the age of 60, seeing a multidisciplinary team, dietitians, physical therapists, other transplant doctors, an infectious disease physician to mitigate the risks of what we call transplant-related mortality or gaining the complications from the transplant afterwards and being able to get people through that process.

Listeners can refer to the podcast we did at the end of 2021 when we went into detail about the Transplant Optimization Program. It's a unique feature of our program. We also use it for autologous transplants for other diseases like lymphoma and myeloma for the age 70 and older and for our CAR T patients 70 and older.

It's a comprehensive program that's run by Dr. Nawas and one of our nurse practitioners, where they give a very detailed and thorough type of optimization for patients undergoing this procedure.

And just two quick things I want to add to what we're saying here in regards to patients being able to utilize transplant more often than maybe in decades past is education and also access. These diseases are not diseases that are cared for oftentimes everywhere. So, it's important for centers like ours, which are a referral center, to team up with referring providers and patients. So, podcasts like this, where patients and their family members get educated about their family member's disease or the disease that they have, these things are important. These efforts are so important because the further and the more reach we have to educating people about these diseases, not only to transplant but also what's available for up-front therapies for their disease.

And then access. Access is a very important thing. Transplant centers are in, oftentimes, big metropolitan areas; and patients get MDS everywhere. It doesn't matter where they are.

The field is making efforts to improve both education and access. To make things easier for people who need to be referred for up-front therapies or for a transplant.

Dr. Patel: One of the questions we oftentimes get from the family members of a patient with MDS, who may not be immediate family members, say a first cousin, an aunt, an uncle, niece, nephews, is what can we do to help? The most helpful thing that could be done is to try and get set up and registered as a potential donor.

Bringing transplant access to our community happens in a lot of different ways, as Satya mentioned. No matter where home is for you that there is a way to access transplant if that's what's needed. It's about trying to make sure that the best donor options are available to anyone that's being considered for transplant. And a huge part of that is expanding the pool of donors that are there.

So, really, that's a very concrete and incredibly helpful way for, a family member to pitch in who may not be immediately considered as a potential donor for their loved one but for the MDS community as a whole.

Dr. Kosuri: That's really important point, especially one of the things that we've noted in the era of post-COVID. It is getting more difficult to not only find matched, unrelated donors that may be in the registry; but also, the matched unrelated donor has to be amenable to the dates that are requested upon them. They have to go through their own medical clearance. The donor process is something that is a detailed process and something that someone has to go through out of the goodness of their heart to be able to donate.

We do need to expand the pool of donors as much as we can, especially in the era post-COVID. It has not been as easy as it was prior, if someone had multiple donors in the registry to be able to utilize those choices.

Jesse: Thank you both so much for the great explanation for all the treatment options for MDS. I want to talk about the future of treatment. Are there emergent

therapies that you're both excited to share with us today? Is there anything on the horizon that's currently in clinical trials that you would like to share with our listeners?

Dr. Patel: Yes, so I had mentioned a couple drugs earlier that are in the context of Phase III trials, meaning in early evaluation they seem to be incredibly promising; and we're now hoping that we can confirm their benefit in MDS. Three medications like that are venetoclax, magrolimab, and sabatolimab.

Another thing that we've seen is we're borrowing a little bit from AML to try and identify the role for what we call targeted therapies, meaning therapies that are effective in subsets of patients with very specific mutations. So currently, when thinking about AML, one example is patients that have a mutation in a gene called IDH1 are eligible to receive a drug called ivosidenib; and those with a mutation in IDH2 are eligible to potentially receive a drug called enasidenib. Both of those drugs are being investigated in MDS in patients that have the appropriate mutation. There's also a large effort underway called the MyeloMATCH initiative which is looking to really refine how we treat patients with MDS based on the mutations that they may have.

So, looking at these targeted therapies, being able to rapidly assess is this effective, is this not; and if it is, how do we then confirm the benefit of that medication and hope to then have it accessible to patients outside of a clinical trial once the benefit has been confirmed?

Thinking about the role of targeted therapies in MDS I think is where our next great advances hopefully lie in terms of how we develop our treatment algorithms and treatment paradigms.

Dr. Kosuri: And so, when we talk about cellular therapies or we talk about immune therapies, patients and their family members will often ask, "Are there cellular therapies or immune therapies for MDS or AML or myelofibrosis?"

One of the original cellular therapy or immune therapy for this group of diseases is allogeneic transplant because it's basically harnessing the donor's immune system to exert disease control and remission for hopefully the rest of that patient's life.

However, as we've talked about during this podcast, not everyone who needs a transplant is able to get a transplant. Whether it's those four legs on the chair. If one of those is missing, then a transplant is not always an option.

In the case there, there are other cellular therapies that are being investigated in this space. Many people have heard of CAR T cells or engineering of the patient's own immune system to go and fight the cancer.

So, we have FDA-approved CAR T-cell or cellular therapy approaches for diseases such as lymphoma and multiple myeloma. And even acute lymphoblastic leukemia, which is a different subset of leukemia from a different lineage. But for AML and MDS, this is something that's still being worked on.

There are early phase studies that are in process right now for the myeloid diseases, specifically AML and also for MDS, where we use various immune system cells to target the blood cancers. So, CAR T cells, for example. There's another cell in the immune system called the natural killer cell, which is also very important. And there's actually a natural killer CAR [CAR NK] that is being investigated for myeloid diseases.

We have a class of agents called bispecific T-cell engagers where it brings the T-cells, which are the soldiers of the immune system together with the malignant cell. It brings them together so the T-cell can fight the malignant cell better. And then there's antibody therapies that target various, what we call antigen or markers. All of these target various markers that define the abnormality oftentimes on a cancer cell.

So even in this space, the cellular therapies, outside of allogeneic transplant, there is movement with earlier phase studies in the realm of myeloid diseases, specifically AML

and MDS. And I think that will be very exciting over the course of the next five to seven years to see what progress we're making in that regard.

Elissa: That's great. It is so exciting to hear that there are other therapies, particularly for those patients who cannot get a transplant. So, it's really great to hear that there is so much stuff on the horizon and targeted therapies, immunotherapies, so that's amazing.

Now a final question to you both. On our patient podcast homepage, we have a quote that says, "After diagnosis comes hope. What would you say to MDS patients and their caregivers to give them hope for the future?"

Dr. Patel: What I would say is our understanding of MDS has rapidly evolved over the last several years, as have the therapies that we can use to treat MDS. We're living in a time where there's a lot of dynamic change when it comes to the landscape of MDS. Many times, patients will come in and see myself, Satya, for the first time; and they may have what's considered higher risk disease or something that they may be very concerned about. Is the treatment that's being proposed going to help me in the same way it may help others or not?

What I always say, or caution is it takes time to collect data, generate data, and then report on that data. And with the pace of research and investigation in MDS, sometimes by the time that data is available, it may not be wholly applicable to the person sitting in front of you.

So, we are at a time of unprecedented change and evolution in how we think about treating MDS, how we think about risk assessing MDS. And the change is in constant motion. Even over the course of 6, 12, 24 months, there can be significant evolution and how we may think about treating the patient.

Dr. Kosuri: Anand, hits the nail on the head. Scientifically, we are moving very quickly for MDS, AML, and other blood cancers.

The other thing that I want to mention, hope comes in many different forms. Groups like LLS educating patients and their family members, allowing them to understand that there's so many things that are available for certain scenarios. That wasn't always the case before. It's usually the doctors would give the patient, "This is what we got, this is what we're going to do", and that's where the stream of information ends.

We're not in that scenario anymore. There are many streams of information, good information like LLS. The other thing that I think is always very helpful in regards to hope for the patients, and one of the things that we try to do in transplant, since it's such a daunting idea to people up front, is that connecting people who have been through the process already. This is super important.

Patients like Ashley who have gone through the transplant are five years out, are sending texts to their physicians about some 5K that they did. She's always volunteered to talk to other patients. And so, this effort is something that we do, and we try to do as much as we can, to allow patients to speak to people who have already been through that process themselves. Because I think that connection and the idea that, hey, this person went through it. They have a similar disease. This is what may be on the horizon, but they got through it.

That is very important, to instill hope in people. So, these types of connections and the education from organizations like LLS and other organizations is something that I think is a very important aspect in regards to providing hope for patients outside of just the physicians and the care teams.

Jesse: Totally agree.

Elissa: That's wonderful. Well thank you so much, and for our listeners, we will have the support resources, education resources at the end of the episode and in the show notes.

Thank you so very much, Dr. Patel, Dr. Kosuri for joining us today. This was a wonderful conversation on MDS, and I hope it does provide so much hope to patients and caregivers that are listening.

We talked a lot about transplant, so I do want to mention that in the show notes, we will have information about Be the Match, so you can learn about signing up to be a donor and help people like Ashley, help MDS patients and other blood cancer patients. Then also your previous podcast, of course, to take a listen to about transplant, GVHD, and also the Transplant Optimization Program at University of Chicago Medicine.

So, thank you again so very much to both of you for joining us today.

Dr. Kosuri: It was fun. Thank you so much for having us. We appreciate it.

Dr. Patel: Yeah, I had such a great time, and thanks so much for the opportunity.

Elissa: Also, a special thank you to The University of Chicago Medicine for supporting this episode 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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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've 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 also find information about myelodysplastic syndromes or MDS at LLS.org/MDS. All of these links will be found in the show notes or at TheBloodline.org.

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