LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Improving Quality of Care for Myelodysplastic Syndromes (MDS)'

Description:

Myelodysplastic Syndromes (MDS) is a group of diseases that have a variety of different treatments and outcomes. In this episode, we speak to Dr. Colin Vale of Emory University in Atlanta, GA, about the treatments for MDS, the potential for transforming into acute myeloid leukemia (AML), and new strategies to give patients the quality of care that they deserve.

Transcript:

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

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

Elissa: Today, we will be speaking to Dr. Colin Vale, a hematologist/oncologist at Winship Cancer Institute and an Assistant Professor of Medicine in the department of Hematology and Medical Oncology at Emory University School of Medicine in Atlanta, Georgia.

He specializes in stem cell therapy and in the treatment of acute leukemia, myelodysplastic syndromes, or MDS, and other hematologic malignancies.

Dr. Vale is passionate about medical education and is the principal investigator for clinical trials for patients with MDS and acute leukemias.

Welcome Dr. Vale.

Colin Vale, MD: Thank you for the kind introduction. I was grateful for the opportunity to meet many patients and their caregivers at the Southern Blood Cancer

Conference over the past two years, so it's wonderful to be working with LLS again. And thank you for all you do for our patients and their families.

Elissa: Oh, well thank you for joining us. We're really excited to have you on the podcast today. And so, our episode today is on myelodysplastic syndromes or MDS. Could you tell our listeners what that is?

Dr. Vale: Yes, so this is a topic that is near and dear to my heart, so thank you for including me to discuss this today. So, before we talk about abnormal blood cell production, I think it is important to first revisit normal or healthy blood cell production, which we refer to as hematopoiesis.

In this tightly regulated and complex process, hematopoietic stem cells and precursor cells differentiate into the healthy, normal blood cells such as platelets, red blood cells, and the various white blood cell subtypes.

Myelodysplastic syndromes, or MDS, develop in the setting of genetic changes to these hematopoietic stem cell and progenitor cells which impacts their growth and development and, ultimately, impairs healthy blood cell production.

MDS encompasses a heterogeneous group of blood cancers, although sharing similar characteristics, including cytopenias, low blood cell numbers, dysplastic, or abnormal cellular appearance, and increased risk of transformation to acute myeloid leukemia, or AML (acute myeloid leukemia).

There are two classification systems for MDS which were recently revised. One is the ICC, or International Consensus Classification of myeloid neoplasms and acute leukemias. There's also the WHO, or World Health Organization classification, and there are some slight differences between these two most commonly adopted classification systems. But hematopathologists and hematologists/oncologists utilize these systems to classify the different subtypes of MDS based off on blast percentage, dysplasia, or defining genetic characteristics.

Elissa: What are the different subtypes?

Dr. Vale: So, there are many depending upon which classification system you use. And, again, they incorporate chromosomal abnormalities, gene mutations, and the number of lineages or blood lines which are impacted.

The classification systems were developed by an international collaboration involving hematopathologists and hematologists looking at the different subtypes of myelodysplastic syndrome, or MDS.

When we think about MDS, we recognize that the majority of the gene mutations and chromosomal abnormalities are acquired, meaning that they develop sporadically or randomly, and more commonly as people get older. The average age at diagnosis is close to 70 years old.

We recognize that there are also some inherited, or what we call germline genetic abnormalities. And Lucy Godley and her coinvestigators demonstrated in an article that was published in *Blood* last year in 2022, that germline predisposition variants can occur in MDS patients of all ages, and that genetic testing should be considered for all patients.

At Emory University, we're fortunate to collaborate with a wonderful cancer genetics group and they've counseled many patients regarding this additional genetic testing.

In terms of what causes the gene mutations, the vast majority of cases it's unknown. We recognize that prior treatment with DNA damaging therapies such as chemotherapy or radiation may predispose to myeloid neoplasms including MDS, whereas other environmental exposures, including toxins such as benzene may contribute, in addition to the heritable predisposition syndromes that we've just mentioned.

Holly: So, Dr. Vale, a question for you. MDS patients listening may have been told that they either have primary MDS or secondary MDS. Could you explain what those are?

Dr. Vale: Yes. So, this is an important distinction both in terms of the pathophysiology of the disease and for risk stratification, which impacts how we select appropriate treatment.

Secondary or therapy related myeloid neoplasms, including MDS, occur following exposure to DNA damaging chemotherapy or radiation which is often administered for treatment of a separate cancer or autoimmune condition.

Elissa: Okay. Now, you had gone a little bit into the different subtypes and chromosomal abnormalities. Do all MDS patients have some type of gene mutation?

Dr. Vale: So the vast majority of patients, well over 90%, will have at least one gene mutation detected at the time of diagnosis, and this can vary depending upon the number of genes which are analyzed or screened. But these genes are involved in normal blood cell production or hematopoiesis, so when a gene mutation occurs, it confers a survival advantage in that cell and that cell then passes along the gene mutation to its progeny through a process that we call clonal hematopoiesis.

Elissa: We interviewed Dr. Lucy Godley of The University of Chicago, just a couple years ago, all about hereditary MDS. Now, as we know, research advances tremendously within a couple years. So, since we talked about the potential hereditary aspect of it, and I'm sure a lot of patients listening are wondering if they got it from a parent or if the disease can be passed down to their child, or if siblings can both get it? Could you explain where our knowledge is at with that right now?

Dr. Vale: Yes, the research by Dr. Godley was critical for understanding of the heritable predisposition to MDS, and we incorporate our cancer geneticists to assist with these conversations, answering these specific questions. What we know is that

heritable MDS can present at any age, and we recommend discussions with our cancer geneticists in all cases of MDS so that they can talk about the potential benefits and risks of additional genetic testing.

This information can be important, especially when we consider stem cell donors for our patients who undergo stem cell transplantation as a treatment for their myelodysplastic syndrome.

Holly: So how is MDS usually diagnosed, and what are the typical signs and symptoms?

Dr. Vale: MDS is diagnosed following evaluation of peripheral blood smear in addition to a bone marrow examination. The bone marrow aspiration and biopsy is critical as we attempt to characterize dysplasia or the abnormal appearance of the different blood lines. Myeloblast enumeration, as there is certain criteria including blast percentage, which helps us distinguish myelodysplastic syndrome from acute myeloid leukemia, while the bone marrow also allows us to test for the chromosomal abnormalities in the different gene mutations that we've been discussing.

Most patients have signs or symptoms related to low blood counts at the time of diagnosis. These are variable but can include easy bruising or bleeding for patients with low platelets. For patients with low hemoglobin or those who are anemic, they may feel more short of breath, feel tired or fatigued, and have exercise intolerance. Patients are also more susceptible to infections, so may present following an infection.

Elissa: You brought this up briefly, but MDS can transition into acute myeloid leukemia, or AML. How often does that happen?

Dr. Vale: So, the likelihood of leukemic transformation can vary greatly. We utilize two main risk stratification models to help us have goals of care discussions and also to select optimal treatment.

The two most widely used prognostic models are the International Prognostic Scoring System Revised, IPSSR, and IPSSM, the molecular stratification. These prognostic models incorporate the severity of cytopenias, or low blood counts, the percentage of bone marrow myeloblasts, different chromosomal abnormalities, and in the case of the IPSSM, the gene mutations.

So, for example, according to IPSSM, the risk of transforming to AML at one year in the very low risk group is 0%. Whereas in the very high-risk group, that rate is as high as 28%. By four years those rates increase to 2.8% in the very low risk and more than 40% in the very high risk, respectively. So, the rates of leukemic transformation can vary significantly over time, and we utilize the different prognostic systems to predict the rate of leukemic transformation.

Elissa: Are there any factors that predispose a patient to be more likely to get AML?

Dr. Vale: Yes. We recognize that there are some higher risk of gene mutations and chromosomal abnormalities in addition to patients with therapy-related, or post-cytotoxic therapy MDS.

Elissa: Now, can this be prevented, MDS turning into AML?

Dr. Vale: Yes. Our goals at the advent of treatment include helping patients live longer and live better. So, we focus on both quality of life in addition to quantity, and we recognize that some therapies have been shown to delay leukemic transformation, including azacitidine, which is a so-called hypomethylating agent.

Holly: So, what are the current treatments for MDS and what factors really go into determining which treatment a patient might receive?

Dr. Vale: For patients with MDS, the treatment options continue to increase. We consider several factors: patients' goals of care, their medical fitness and comorbidities or other chronic medical conditions, the severity of their symptoms, there's stem cell transplantation candidacy, and the aforementioned risk stratification, the IPSSM and

IPSSR when we're selecting the optimal treatment approach. We always consider clinical trial options as well, where we examine new or novel approaches to try to improve outcomes for patients with MDS.

So, we employ a multidisciplinary clinic which optimizes supportive care including transfusions, iron chelation, if there's evidence of trans fusional iron overload, nutrition, psychosocial support are standard of care for all of our patients.

For patients with lower risk MDS, again defined by the risk stratifications that we've been discussing, there are several options including observation, use of erythropoietin stimulating agents, luspatercept, lenalidomide, especially in patients with abnormalities in Chromosome 5, and azacitidine.

For patients with higher risk disease, azacitidine and other hypomethylating agents including decitabine and Inqovi® can be considered. Recognize that an allogeneic stem cell transplant represents the only potentially curative treatment approach. And the American Society for Transplantation and Cellular Therapy recently released new practice guidelines as it relates to care for patients with myelodysplastic syndromes.

Elissa: Patients can also be on just a watch and wait protocol, correct?

Dr. Vale: Correct. So, that is a discussion for patients with lower risk disease with minimal symptoms related to the disease and also without any transfusion needs.

Elissa: How does that end up going? So, if you have a conversation with the patient and you say that "Hey, we could just do some active monitoring, what's called watch and wait?" I would think that that may increase their anxiety a little bit not thinking that they're getting treatment right away for cancer.

Dr. Vale: Yes, that is an excellent question, and certainly one that we hear in clinic often after we inform patients that they have a blood cancer and then recommend watching, which we recognize that the supportive care strategies that we previously discussed including ensuring optimal nutrition and psychosocial support, antimicrobial

therapy are all components of managing MDS even if there is not an MDS directive therapy at the onset of diagnosis.

But we have these discussions with patients about the potential risks and benefits of the different therapies so that the patients can make the most informed decisions regarding their treatment.

The course of MDS can be unpredictable, so we are continually reassessing the potential benefits and optimal therapies at each clinic visit.

Elissa: We actually talk about shared decision making quite a bit on this podcast. It's good for the patients to understand the side effects of the treatments and also weigh those benefits or risks against a watch and wait protocol, right?

Dr. Vale: Correct, because the different therapies are all associated with a different side effect profile. So, it is important to discuss that as we're determining the optimal treatment approach.

Elissa: Now, can patients potentially be watch and wait for the rest of their lives?

Dr. Vale: So, there are a number of factors which impact that decision including a patient's age and their comorbidities in addition to the risk stratification. When we think about the median age of diagnosis of 70, for patients with lower risk disease and other chronic medical conditions, we may end up just monitoring their MDS for several years, especially if we believe that the potential risks of treatment outweigh potential benefits. But the vast majority of patients with MDS will require treatment at some time over the course of their life span.

Elissa: So, let's talk about emerging treatments. Are there any coming out, or on the horizon that you're particularly excited about?

Dr. Vale: So, as a field, we remain committed to helping more patients live longer and better lives while we also seek to minimize treatment-related side effects. There

are several ongoing studies investigating combination therapies, so they try to build off of the azacitidine monotherapy or backbone, including the bcl-2 inhibitor venetoclax, which has already been approved for use in patients with acute myeloid leukemia.

At the most recent American Society of Hematology®, or ASH, meeting, data from the Phase 3 IMerge trial investigation imetelstat, a telomerase inhibitor, were presented, and these were very promising results.

There are a number of ongoing clinical trials investigating immunotherapy and cellular therapies including bispecific antibodies, and there are many other clinical trials which are attempting to improve results in the post-transplant setting as well.

At Emory University we are fortunate to be able to offer new and novel approaches to treat MDS through our clinical trials program, and with ongoing collaboration, we're confident that outcomes in patients with MDS will continue to improve.

And what it showed in patients who were transfusion dependent, who were either ineligible for or had been exposed to an erythropoietin stimulating agent, which is often one of the initial treatments for patients with MDS who are anemic. This trial showed that there was a benefit in patients who are treated with imetelstat. And symptomatic anemia remains an ongoing challenge for the treatment of many of our patients with MDS, so the addition of more therapies which demonstrate an improvement related to symptomatic anemia is vital.

Elissa: That's great. Now, on our patient podcast home page we have a quote that says, "After diagnosis comes hope." What would you say to patients and their families to give them hope after a diagnosis of MDS?

Dr. Vale: So, as I mentioned earlier, the field of hematologists and oncologists treating MDS remains committed to improving outcomes, to help our patients with MDS live longer and better lives. We're fortunate at our institution to work with many

different providers with a multidisciplinary approach to ensure patients with MDS are receiving the care that they deserve.

We are also incredibly lucky to partner with The Leukemia & Lymphoma Society to ensure that our patients are supported throughout every step of their journey. And, as we just discussed, we continue to see encouraging results related to the treatment of patients with MDS every day, and we're hopeful that we'll be able to help more patients each day in the future.

Elissa: That's wonderful. Well thank you so much, Dr. Vale, for joining us today and talking all about MDS. It is exciting to hear these potential treatments coming out of ASH (American Society of Hematology) and of clinical trials that will really provide hope to patients with MDS. So, thank you again so very much for joining us today. And for, of course, all of your support for The Leukemia & Lymphoma Society.

Dr. Vale: Thank you for having me and I look forward to seeing you again in the future.

Elissa: And thank you to everyone listening today. *The Bloodline with LLS* is one part of the mission of The Leukemia & Lymphoma Society to improve the quality of lives of patients and their families.

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You can find more information on myelodysplastic syndromes at LLS.org/MDS.

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