Episode: 'Myelodysplastic Syndromes (MDS): A Group of Diseases'

Description:
Please join us as we speak to Dr. Daniel Pollyea from the University of Colorado School of Medicine. In this episode, Dr. Pollyea discusses the group of diseases that make up Myelodysplastic Syndromes (MDS) and how their variability leads to different treatments and prognoses, from active monitoring to chemotherapy and/or stem cell transplantation. He shares his excitement about new treatment advances and is looking forward to an era of innovative targeted treatments for MDS.

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 to Dr. Daniel Pollyea, the Clinical Director of Leukemia Services and Associate Professor of Medicine in the Division of Hematology at University of Colorado Medicine. His work focuses on understanding the nature of leukemia stem cells and developing drugs that target this population to potentially allow for curative therapies.

Dr. Pollyea has served as the principal investigator for multiple early phase clinical trials and currently serves as Chair of the National Comprehensive Cancer Network (NCCN) Guidelines on acute myeloid leukemia.

Welcome, Dr. Pollyea.

Daniel Pollyea, MD, MS: Thank you so much for having me.

Elissa: So let’s get started with learning a little bit about you. How did you start in the field of medicine and then studying leukemia and myelodysplastic syndromes?
**Dr. Pollyea:** Well, as far as the field of medicine, I always had a sense that I wanted to be a doctor. My father is a primary care doctor who took care of a lot of patients in sort of an underserved area when we were growing up, and is passionate about what he does, and it was hard not to be inspired by that. And I really took my cues from him in terms of valuing everything there is about this ability to help take care of patients when they're in their biggest time of need.

And I think that's what ultimately really did attract me to oncology is that privilege of being able to help people when they most need help and to guide them through what's for most people or many people the most difficult journey of their lives.

As I kind of navigated through training, it was obvious to me that the myeloid malignancies, AML and MDS, were the most fascinating of the cancers that I was exposed to, and on a sort of research and biological level, really, really interesting to learn what makes them tick, and huge opportunities to improve outcomes for these patients because, historically, we've done so poorly in treating them. And so, all that sort of led to a career in this field really.

**Elissa:** That's really great. There is so much that can be done for leukemia, acute leukemias, MDS. Now today's episode is on myelodysplastic syndromes, or MDS. Could you tell us what that is?

**Dr. Pollyea:** Yeah, myelodysplastic syndromes, or MDS, is a type of a blood cancer. It's actually a group of diseases that has some variability or differences within the group, but they are all similarly types of cancers that affect the bone marrow. The bone marrow you can think of sort of like the organ that is responsible for making all the cells of the blood. And so, when cancers occur in the bone marrow, it can cause the failure of the bone marrow to properly function.

And since the bone marrow makes red blood cells that carry oxygen and make you feel strong, and platelets that clot the blood, and white blood cells that fight infection, cancer of the bone marrow or failure of the bone marrow can cause all kinds of
problems, ranging from bleeding to infectious complications. And that's many times, or most times how MDS can manifest. But, when you come down to it, even though there are a lot of different flavors of MDS, they're all a type of cancer that affects the bone marrow.

Elissa: Now what is the incidence rate? Is this a very common blood cancer?

Dr. Pollyea: This is an uncommon cancer. When you compare incidence in this country to things like colon cancer or breast cancer, prostate cancer, MDS is very unusual. Probably only 20,000 to 30,000 new diagnoses made every year. There's a lot of reasons why those numbers are inaccurate, but it's probably somewhere in that neighborhood.

In terms of blood cancers, it's not a terribly uncommon form of a blood cancer. It's not as common as other sort of things like lymphomas or multiple myeloma, but it's not super uncommon when you just look at blood cancers. But when you compare it to the incidence of just cancer in general, it's quite uncommon.

Elissa: Now that 20,000 to 30,000, is that just in the US or is that around the world?

Dr. Pollyea: Right. That's in the United States, yeah.

Lizette: Wow! And I know that there is primary and secondary MDS. Could you explain that difference?

Dr. Pollyea: Yeah. So, secondary MDS is usually what we're talking about here as what we would call treatment related MDS. So, those terms are sort of interchangeable when it comes to MDS. And what that means is that nowadays, when oncologists are so good at treating other types of cancer with chemotherapy and radiation, many times patients can be cured or live a very long time after their treatment, but these treatments, certain types of chemotherapy and radiation, can actually cause an MDS to occur. That's a horrible thing to happen. But that can happen, and we refer to those as secondary MDS or treatment related MDS.
And that's opposed to primary MDS. That's a situation where MDS happens, but we don't really have an easy explanation for why. The vast majority of patients fall into that category. And we just don't really understand why a particular patient developed MDS, and it's outside of exposure to chemotherapy or radiation for another cancer.

**Elissa:** Now are there gene mutations like there are with other cancers, like AML, that could potentially cause MDS to happen?

**Dr. Pollyea:** Yes. So, this is an important concept to sort of understand. Almost every patient with MDS, when we look at their MDS cells, we are going to find at least one, if not several, mutations in those MDS cells, but those mutations are not mutations that the patient was born with, and they are not mutations that if we looked at the healthy cells we would find. They're not mutations that they inherited, and they're not mutations that they can pass along. These are mutations that are restricted to just the cancer cell population in their body.

So, it's an important distinction to know that, as opposed to other subtypes of cancers where there are inherited mutations that are set up for the development of a cancer. That can happen in MDS. It's quite rare, but that can happen in MDS, but the usual situation is that those mutations that do occur in MDS are present just in the MDS cells not in the normal healthy cells.

**Elissa:** So, I'm curious. I'm an AML survivor-

**Dr. Pollyea:** Oh.

**Elissa:** -and I had inversion 16 mutation. But it went back to normal after the chemotherapy was finished. Is that something that can also happen with the genetic mutations in MDS once the treatment is finished, for those mutations to go back to normal?

**Dr. Pollyea:** Absolutely. So, when we can take a chromosome abnormality like an inversion 16 in AML or another chromosome abnormality that can happen in MDS or a
gene mutation that happens in MDS and deliver a treatment, and then repeat that testing and not see any evidence of that abnormality, then we can be very confident that we are in a deep remission. And, certainly, in order to be cured of these diseases, we would have to eradicate all evidence of those chromosomal abnormalities or mutations. And so that is something that we do look at as a surrogate for how deep our treatments are or were or can be. It's definitely an important thing to monitor.

**Elissa:** Now what are the signs and symptoms of MDS and how does one usually end up getting diagnosed with MDS?

**Dr. Pollyea:** MDS, as a cancer of the bone marrow, something that causes essentially the failure of the bone marrow, can result in clinical symptoms that are not super specific. So, the most common thing we hear is that people are more tired and fatigued, and that is from anemia, and that can just be sort of different for everybody. One person can be really significantly affected at a certain level of hemoglobin that another patient doesn't really have symptoms at. So, but that is a very common symptom at presentation.

Other manifestations of anemia can be things like shortness of breath, particularly with activity. It can be dizziness, lightheadedness, particularly withstanding up from a seated position; even passing out in those situations. All of those can be reflective of anemia.

A person might not make enough platelets because of their MDS and that can manifest as a bleeding problem. So, spontaneous bleeding or, or really easy bruising can be a common symptom at diagnosis.

And then also, because it, can affect the white blood cells and your ability to fight infection, having MDS can result in immune suppression and more susceptibility to infectious complications. So, I'd say those three clinical areas are the main symptoms at presentation.
**Elissa:** Since a lot of those symptoms are similar with other blood cancers, what distinguishes MDS from the other blood cancers?

**Dr. Pollyea:** Right. So, in the end, just looking at somebody's bloodwork and seeing that they are deficient or low in these different levels would not be diagnostic of MDS because, as you mentioned, a person can have a multitude of other problems in the bone marrow. They can have cancerous problems or even noncancerous problems in the bone marrow. So, ultimately, a bone marrow biopsy is required to make this diagnosis. And an experienced hematopathologist can look at the sample under a microscope and through a variety of different means tell clinicians, physicians that this is a case of MDS or something else that would need to be separated out.

**Elissa:** Are we looking a lot also at blast percentages? For our listeners that don't know, the immature cancer cells that are just replicating, so the blast percentage in the bone marrow?

**Dr. Pollyea:** Absolutely. So when we're looking at any of the myeloid malignancies, so specifically here AML or MDS, one thing that we're focused on is what's the percentage of cells in the bone marrow that are blasts or, as you said, really immature cells because we say that once a person's bone marrow is made up of 20% or more blasts, then their diagnosis is AML, whereas MDS has to be less than 20% blast, so the blast percentage is really important.

Some MDS patients don't have any increase in blasts.

**Elissa:** Oh!

**Dr. Pollyea:** Other MDS patients might have, you know, 15% or 10% or 7%, 12%, but anything below 20% can be MDS. Anything above 20% has to be AML. That's kind of how we make these distinctions.

**Lizette:** Sure. And I know that some folks really think that all MDS patients, their disease will evolve into AML. That's not correct, right?
**Dr. Pollyea:** Right, yes. Statistically, only about a third of patients ultimately will go from MDS to AML. And so, what people need to understand is that MDS is really a spectrum of diseases. We call it all one thing, but it’s a spectrum of diseases, and a person can have MDS that is just about to evolve to AML, acute myeloid leukemia; but on the opposite end of that spectrum, MDS can behave itself for many, many years, even a person’s entire lifetime, with no treatment at all.

So, it's really important to understand when you're diagnosed, where are you on that spectrum because there's a major difference in how we would regard it or treat it. It's a major difference with respect to just expectations and prognostication and things like that. That's why we really emphasize MDS is not one disease, it's many diseases.

**Lizette:** Right. And I'm sure you get asked all the time from an MDS patient, "How does it look? Does it look that I will evolve into AML?" I think that's a tough question to answer, right?

**Dr. Pollyea:** It is a tough question to answer. On an individual basis, I would say it's an impossible question to answer because we can't know on an individual level what's going to happen to one person.

What we do have is a prognostic scoring system called the IPSS-R. It's soon going to change to the IPSS-M, but this IPSS-R system, we can use it to plug in information about one individual and see based on the experience of hundreds that are in this model, what is the percentage chance that this individual would evolve to AML, and what is the percentage chance how long might this patient live?

Now I really discourage people from using this to sort of try to make a direct prediction about an individual patient because so much variability in individual patients. But these are tools that are useful for mostly us on the practitioner side to get a general sense of how aggressive one patient's disease can be or is, but that prognostication is something that your doctor should perform to get that sense. But when you hear
those numbers, it's not like a guarantee of what's going to happen to you as an individual because that is just very variable.

**Lizette:** Sure. And I think that that's a really important point to bring up. And like you said, it's even an umbrella term really. There's different types of MDS and different genetic mutations that may affect the prognosis, right? Is it just the genetic mutations? Is it also how somebody will react to treatment?

**Dr. Pollyea:** Right. So that IPSS-R score currently takes into account a couple of different variables to make some predictions about how responsive a person’s disease might be to treatment, what's the likelihood that they’re going to evolve to AML. Those factors that are taken into consideration include how low are the blood counts, what are the chromosome abnormalities if they exist in the patient, and what's the blast percentage in that individual patient?

At the moment, like right now, today, we don't have a way to incorporate the gene mutations like you suggested into this prognostic model, but this was just presented at a major meeting in December, and we're awaiting the peer review and publication of a model that will do this. And that should really be almost any day now that we'll be using that, and that will allow us to incorporate gene mutations into this prognostic model, and it'll help improve our ability to prognosticate for MDS. So that's something that's coming soon.

**Elissa:** Wow, that will be great to be able to include those as well, and really get a general picture. Is there a general prognosis for MDS patients, or is that kind of all across the board?

**Dr. Pollyea:** Yeah, there's no real way to generalize because things are so heterogeneous. I mean, for some people they're on the doorstep of AML, and other people will never need treatment the rest of their whole lives. So, it's impossible to generalize it. That's why it's so important to get all this information about an individual's disease at diagnosis from the bone marrow, and then get a sense of,
what's the sort of general prognosis for an individual patient? And I think that is really helpful information.

**Elissa:** Yeah, it's very interesting that you said that some patients might not need treatment. So are they going into kind of a watch and wait type protocol, active monitoring?

**Dr. Pollyea:** That's exactly right. So, it's an unusual situation to be in to be told, "Hey, you have cancer but we're not going to treat it." And that's not something that you would ever really hear from my colleagues who treat solid tumors, right. I mean, for the most part, the presence of a solid tumor warrants treatment. But with MDS, for a variety of reasons, that can be in the cards that we don't really treat it. And those reasons include that this is a disease that we wouldn't expect to progress very rapidly, that we would expect to kind of smolder along for a very long time and, frankly, unfortunately, it's also reflective of the fact that we don't have great treatments a lot of times for MDS patients. And so, if we don't have really great treatments, sometimes it's better to just observe a patient. So, it's a mixture of a bunch of different factors.

But, yeah, it's a little hard sometimes to grapple with this odd scenario where someone's telling you, you have a cancer but we're just going to watch it.

**Elissa:** Yeah, especially since it is somewhat closely tied to AML, which is usually something where you need treatment very, very quickly. And so that just seems so different to know that there's MDS patients who might not need treatment at all.

**Dr. Pollyea:** That's right, yeah. And, yes, you're right. I mean MDS and AML are definitely in the same family, but not all MDS patients will progress to AML. And so, figuring that out, or getting a good sense of how likely that is for an individual patient is really crucial because that is the difference between making a decision to say, "Hey, we really do need to treat this," versus, "You know what, let's just kind of keep an eye on things for now."
**Elissa:** Now you mentioned a lack of treatments some of the time. What are the current treatments for MDS, and what is on the horizon that you're excited about?

**Dr. Pollyea:** Yeah, a great question. Right now, the landscape is still limited, so the main treatment for most MDS patients is what we would call a hypomethylating agent, which is a low dose chemotherapy treatment. There are two that are approved; one is called azacitidine, the other is called decitabine. And they're fairly equivalent, these two treatments. There's some difference in how they're delivered. One has an oral formulation, others are IV. But that's been the mainstay of treatment for MDS for a long time.

Unfortunately, only around 30% or so patients respond to that treatment when they're given it, and it can take four to six months for them to actually show a response if they do respond. So it's a frustrating treatment to have to give.

There are other treatments that are approved for different subsets of patients, so particular patients with an abnormality called a deletion 5q; that’s a chromosomal abnormality. We give them a pill called lenalidomide. So that's one subset that's treated a little bit differently.

There's another group of patients with a gene mutation called SF3B1. We give those patients a treatment called luspatercept. So that's a little bit of a different carveout for those subtypes.

Other patients, we don't necessarily treat their disease per se, but we give them medicine to sort of stimulate their bone marrow to make red blood cells. Treatments that we all erythroid stimulating agents. So those can sometimes be appropriate.

Right now, that's sort of the landscape for how we treat MDS. You asked about the future, and I think we’re all really excited about new therapies that are coming in the field of MDS. There are currently several very promising clinical trials that we hope to hear results of in the coming months to years that I think could really change things.
**Elissa:** Yeah. The landscape of blood cancer treatment in general, I feel like has advanced so much in the last two years that it's really exciting to see what could come next year or the year after that and really help these patients out.

**Dr. Pollyea:** Yeah. A lot of these advances are because of LLS and the support from the community, and we've really just made tremendous strides partnering with groups like LLS and others to bring forth all these really outstanding, exciting new developments.

**Elissa:** Now I'm sure a lot of patients or caregivers listening have heard about CAR T-cell therapy and targeted treatments, precision medicine. Are things like that potentially coming down the line where we could have more targeted therapy for MDS?

**Dr. Pollyea:** Yeah. I definitely hope that the era of more targeted therapy for MDS is coming. I'm not sure how quickly that will encompass CAR T or other immune therapies for this disease. We're trying hard on all those fronts, but there's a lot of challenges there. And we haven't had too much success so far; not that we're going to stop trying, but those efforts haven't been as successful as with our lymphoid malignancy's colleagues or our ALL colleagues, but we hope to get there. I think there's a lot of things to be excited about, though, independent even of immune therapies that we'll be exploring or are being explored right now in the field.

**Elissa:** That will be really, really neat.

**Lizette:** And I know Dr. Pollyea that over the last couple years there's been more advances for MDS. I know that there's two different drugs, the decitabine that you mention and cedazuridine.

**Dr. Pollyea:** Yeah, so, that combination allows us to give a medicine called decitabine, which is one of those low dose chemotherapy treatments; it's been the mainstay of MDS for a long time. It allows us to give it orally. So that second drug you mentioned basically allows the decitabine to not get deactivated in the intestinal
system and, therefore, allows it to be active even when taken as a pill. So that combination is now approved for MDS patients and it's an oral option which is really nice.

**Elissa:** So, what about stem cell transplants? Is that something that is used very often with patients, or what makes an MDS patient a good candidate for that?

**Dr. Pollyea:** Yeah, that's a great question. So, stem cell transplant remains the only curative therapy for MDS that we have. Now, if a person could live their entire life with MDS and not need to be treated, then I would argue that we don't really need to do anything to cure their disease, and anything that we do there is potentially dangerous and toxic.

So, selecting the appropriate patients for a treatment like a stem cell transplant, which is still a pretty risky thing to do, is really important. So, we usually reserve stem cell transplant in MDS patients for those that have really aggressive disease features and are pretty clear to be evolving to or on the doorstep of AML.

And in those cases, sure, it's appropriate. We really don't do well with transplanting most people past their late seventies, so that's still a bit of a barrier. Not that there's a black and white age cut off, but, you know, getting into the eighties, it makes it really hard to do a transplant for a variety of reasons, and a patient really has to be in pretty good shape to be able to tolerate something like a stem cell transplant. So, making sure that a person is a good candidate and will be able to tolerate everything involved is a pretty crucial part of the process.

**Elissa:** Right. So, what happens with the older population then who may not be a good candidate for a transplant?

**Dr. Pollyea:** Yeah. Well, we try one of the treatments that we discussed if they're an appropriate candidate for treatment, if we think that they need a treatment. And then
we hope to be able to get their disease under control or into a remission and keep them there for as long as we can. That's really the goal.

**Elissa:** That's great. So, to finish up our podcast 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 families to give them hope after a diagnosis of MDS?

**Dr. Pollyea:** Yeah. I like that message. I completely agree with it. What I would say is that we are doing so much better now than we did just a few short years ago in terms of successfully treating these patients and having various options for them. There are many other treatments that are coming right around the corner that I think will make us even better at this. And I'm really glad to hear that people are optimistic about the future because on our side, on the clinical and research side, that's definitely how we feel.

**Elissa:** Well, thank you so much, Dr. Pollyea, for speaking with us today and telling us all about MDS and the future. I think there is so much excitement to hear about these new potential treatments coming out. I know that LLS will keep reporting on those as they are approved. We definitely encourage our listeners to ask their doctor about clinical trials, so maybe they might be able to get in on one of those. But thank you so much for speaking with us today. This was so helpful, and I think gives a lot of hope to patients.

**Dr. Pollyea:** Thank you so much for having me.

**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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We would also like to know about you and how we can serve you better. The survey is completely anonymous and no identifying information will be taken.

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 about MDS at LLS.org/MDS. All of these links will be in the show notes or at TheBloodline.org.

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