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Dr. Christopher Lowrey: It's a real honor to be here today with all of you and really appreciate the sponsorship of the MDS Foundation. This is really important work.

So, what I'd like to do today in my lecture which will take about 20 minutes and then I'll give you time for any questions you might have is to kind of educate you on what MDS is. Most people have a pretty good idea of like what high blood pressure is or diabetes or heart disease, things like that, but MDS is kind of esoteric. Most people haven't even heard of Myelodysplastic Syndrome, or MDS, and it's actually a pretty complicated topic even for doctors, even for hematologists. A lot of research is going on to really try and understand it, but today I'll give you kind of an introduction into what MDS and why it happens, why people get MDS.

So, this first slide kind of defines what people notice when they have MDS. So, it's usually about low blood counts. That's what brings a new patient who's come down with MDS to their doctor or care provider. They might have low red blood cells and they have that. They usually feel fatigues and shortness of breath when they do things like going up and down stairs. They might have low white blood cells and that can lead to frequent or unusual infections that most people who don't have MDS probably wouldn't get. They can have low platelets and the platelets help clot the blood and they can have abnormal bleeding and bruising and then sometimes, an important thing to know, is that MDS can progress to leukemia in some cases. So, we'll talk about all these different things and why this happens.

So, I'm going to start out by not telling you actually about MDS, but telling you how normal blood cells are made because you have to understand how the normal process works before you can understand what goes wrong in Myelodysplastic Syndrome.

So, if we were to take blood from any of you and put it on a slide and look under the microscope this is what we'd see right here and… so these red things here these are the red blood cells. They're round and they make up most of the blood cells and they're the ones that carry oxygen. So, that's a really important job. All these kind of purple things are the white cells and they're not white because we stain them when we look at them under a microscope and that makes them kind of purplish, purple or blue or red and these are all the different types of white blood cells that we have in our body and they all do different jobs mostly to help fight infection and then you can see this little guy right here. That little cell right there is a platelet. So, if for example, you cut your finger maybe on a knife when you're cooking dinner, all those little platelets will come right to the place where the cut happens and make a plug and that'll stop the bleeding. So, they're really important, too.

So a really important thing in understanding how blood cells are made and understanding MDS is that all blood cells come from what we call a stem cell and my guess is you've all heard of stem cells. It's really hot these days. Stem cells are involved in a lot of different diseases and a lot of treatments for diseases are coming from stem cells. A lot of really hot research. The very first stem cells that were ever discovered were the blood stem cells that live in our bone marrow and what this shows is that this cell right here that's a petrivous (sp? 3:55) stem cell, actually a drawing of a stem cell, gives rise to all these other cells. So, these on the far end of the slide these are the cells that are in the blood, but they all come through a series of steps from this very common stem cell. Does that make sense to everybody?

So, this is a picture of some actual stem cells we isolated in my laboratory, but these are normally they live in the bone marrow and there's some interesting kind of facts about stem cells. If you go into the bone marrow where the blood is made only one in 10,000 cells is a stem cell. So, they're very rare and at any time only a few stem cells, probably less than 10, are giving rise to all the blood cells in our body. The others are resting. They're kind of waiting until they need to be called upon. In mice, this has never been done in humans, but in mice you can take one stem cell and regrow the whole blood system. It's just amazing that one cell can regrow everything. These stem cells that we're talking about they're really unique because not only do they give rise to all the other blood cells, but they can self-renew, not shown here, so that they can regenerate more stem cells and no other cells in the body can do that. So not only do they give rise to all the blood cells, but they can make more of themselves if the body needs that and these are the exact same cells that we use in a bone marrow transplant whether it's a transplant from a patient's own bone marrow or from a donor like a brother or a sister or an unrelated donor, these are the cells that do the magic, these stem cells because they can regrow the whole blood system.

So, the next slide shows where blood cells are actually made in the bone marrow. In children like babies and young children, all the bones in the body have active bone marrow where blood is made, but this is a picture of an adult skeleton and this shows where the bone marrow is active making blood. So, it's in the hip bones, it's in the shoulders, it's in the ribs and it's in the spine mostly, a little bit in the upper leg bone and if you look inside of a bone like in this drawing you can see that this is where the bone marrow is. If you ever took a chicken bone or maybe the next time you're eating chicken just break it open and you can look inside and you can see the bone marrow. It's right in there. And as some of you in the audience know when we do a bone marrow biopsy to take a look at the blood being formed the place we do it is we call this posterior iliac crest or the hip bone and that's where there's lots of really active bone marrow. So, that's one reason why we go there and do it. Another reason is there's not many pain nerves, there. So, in the old days they used to do it in the sternum or the rib bone and that was pretty gruesome, but I think this is a lot better here to do it there.

If you have any questions just go ahead and raise your hand any time.

So, if any of you or any one has a bone marrow biopsy you might have been shown when it was done by the nurse or the doctor who's doing it that we take a little tiny piece of bone, it's about as big as a grain of rice, but when we look at it under a microscope it looks pretty huge and this is what we see when we look at a piece of a bone marrow under the microscope and this part is actually little pieces of bone that is in the center of the bone and this is the actual marrow, this stuff here, and you can see it's about half made up of fat. That's the white area and about half of cells. That's the pinker area and those cells are the developing blood cells. So, if we take our microscope and zoom way in now then this is what we see and it's kind of neat. It's a whole jumble of immature cells being formed in the bone marrow. So, these are the exact same slides I use for the medical students. So, they have to learn all the names of these little cells here, but these are all the developing cells kind of jumbled in. So, like these are immature white cells and these are immature red cells and then down here these are the immature platelets that are forming. So, this is what we see when we actually look at a bone marrow biopsy.

So, what we're looking for there is we like to look and see the development of the blood cells and you can see all the way from the stem cell and then through a series of steps you go from the stem cell all the way down to a mature blood cell. Most of these steps occur in the bone marrow and then when the cells are ready to come out they come out into the blood. You can kind of think of this as these stem cells these are kind of like the baby cells. There's no truth to the rumor that this is a picture of Dr. Hill (laughing) who will be giving the next lecture and so those are the baby cells and then these are a little more mature. You might think of these as teenage cells, but clearly these are not ready yet for prime time, but the final cells they're ready to come out of the bone marrow and go to work and I chose a picture of this fellow who's a Navy Ranger and that's because the white blood cells go out and help fight infection. So, you can kind of think of it as this maturing of the red cells… of the white cells in the bone marrow as kind of like growing up just like you'd think of a person going through the stages of development.

The exact same thing happens for red cells. So, here are red cells starting from a stem cell and going all the way through the steps to get a mature red cell and you can see it gets smaller and it actually loses this thing here. This is the nucleus that comes out of a red cell and then the platelets do the exact same thing. They also go through a series of steps and they're kind of neat. At the very end these cells explode into all these little tiny platelets, but the point here is they, too, go through all these different steps. One way to think of this is it's kind of like a car factory. You can see just like the different stages of the blood cells being developed. It's almost like going down an assembly line, automobile factor, where you might put in the engine here and put on the doors here and put the battery in here and all this kind of stuff so that by the end you go from just a car body to a final car ready to go down here at the end just like you go from an early blood cell to a blood cell that's ready to go. So in MDS, what happens is this process, this step by step highly orchestrated, complicated process gets blocked in some way or becomes less efficient and that's what that red X is there to indicate.

So, why does this happen? So, people have known that in Myelodysplastic Syndrome what goes wrong is the cells just can't go through this normal process. We call it differentiation, but why does that happen? So again, we have to step back and talk about what happens in normal cells and the first thing to understand is DNA that you've all heard of DNA. You've all heard of genes. Genes are pieces of DNA that live in the nucleus of all the cells in our body and what they do is they provide the instructions for making protein. So, here's a protein and proteins are the machines that do all the work in our cells. Everything that's done in our body is done by proteins and for example they make it so that blood cells can carry oxygen, fight infection, clot the blood. Without the right proteins, you can't develop the blood cells and they can't do their job normally. Does that make sense to everybody? So in MDS what happens is you get damage to the genes. So, if the genes are damaged then they don't tell the cell how to make the proteins. So, the proteins aren't made or they aren't made correctly, so they don't function correctly. So, that means fewer of the mature blood cells are made or they can't do their work, so they can't carry oxygen effectively or fight infection or clot the blood like they should. So because of these mutations, you get low numbers of cells and then sometimes the cells don't work right. That's kind of like the hallmark of MDS.

How do these mutations come about or in other words how do people get MDS? So, one way that the DNA can be damaged is from exposure to chemicals. So, we have a patient we think might have MDS. We'll often ask them have you ever worked in a chemical factory? Have you worked around an oil rig or something like that where you're exposed to toxic chemicals? So, there are certain known chemicals that can actually damage the DNA if you have exposure to them over a long time. This isn't common. Most people that's not involved. Another thing is radiation can damage the DNA. So, we'll often ask did you work in a nuclear power plant? Did you work in a lab that used radiation? Did you work in a nuclear submarine? Things like that where people might be exposed to radiation. Again, very rare that those things play a role.

Something that is more common and related, though, is that certain forms of chemotherapy while treating cancer can actually damage the DNA. In fact, that's how they work. They damage the DNA so much in cancer cells like a breast cancer cell, a lung cancer cell, a colon cancer cell that the cell actually kind of commits suicide. That's what you're trying to do, but can also damage the DNA in your stem cells, in the bone marrow stem cells, and that's not a good thing because in relatively rare cases it can go on and lead to Myelodysplastic Syndrome and the same with radiation therapy. Patients who have radiation therapy for cancer are also at slightly increased risk of coming down with MDS in the future because the stem cells get damaged, but in most cases there's nothing like this. There's no smoking gun. It's really just bad luck. Every minute we are making millions of blood cells, new blood cells in our bone marrow. It's incredible how this happens. Just think of that. Millions… You're sitting here. Your bone marrow is cranking out a million cells in the last minute and every time it makes a new cell it has to remanufacture the DNA, copy the DNA and it's just going to make mistakes. The three million… I think it's three million. Three million bases of DNA in every cell and it has to copy those three million and mistakes are made. Most of the time those mistakes don't have any consequence. The cell just lives its normal life and dies and the mutation is gone, but in rare cases just by bad luck a mutation can be made that leads to Myelodysplastic Syndrome. So, most of the time it's just bad luck that people come down with this.

So, going back to our analogy of the assembly line in a car factory if you have damaged genes in your stem cells then you have bad instructions. So, it's almost like you're telling the workers don't know what to do in the factory. They start making mistakes as the cars come down the assembly line. So, they might use the wrong parts or forget to put a part in and so the assembly line might grind to a halt or slow down or the cars that come off it at the end might not work very well. That's really what happens in MDS. Instead of cars coming out at the end of the assembly line, it's blood cells, but they don't work and we have fewer of them.

So, the final thing I wanted to present and address is why do some patients who have MDS go on to develop leukemia and it's really kind of just a numbers game. So, this is normal where you have your DNA, your protein and you make a normal number of cells. In MDS, you have a few mutations like we've talked about. Those effective proteins and you make fewer cells. So, that's MDS where you have low numbers of blood cells, but in leukemia, patients who develop leukemia, tend to acquire more mutations than you had just with the MDS and one reason is remember I said some of the proteins don't work. Some proteins prevent us from getting mutations in our cells and actually fix mutations if we do get them, but if those proteins stop working in MDS, then were a patient who has MDS is more susceptible to get even more mutations and if some of those hit certain important genes then the cells instead of being too few, now there're too many and they start to grow out of control and that's what leukemia is – uncontrolled growth of blood cells. So, it's not a common thing for MDS people to get leukemia, but this is when it happens this is how it happens.

Okay. So, that's my introduction to MDS. I'll be glad to answer any questions except I'm not going to answer any questions about that guy. So, does anybody have any questions? Yes.

Q1: You haven't mentioned the word 'blast.'

Dr. Christopher Lowrey: So, the question was about blasts and it's a little tricky the definition of blast. We all have blasts in our own bone marrow and they're one of those stages going from the stem cell to the mature cell. One of those stages is actually the blast stage and normally we should have five percent or less blasts in our bone marrow, but as you get MDS or even as you go onto leukemia typically you have more and more blasts. So, the definition of leukemia is 20 percent or more blasts in the bone marrow. That is leukemia. If you have between five and 20 percent that means you have Myelodysplastic Syndrome. So, it's kind of a continuum along the way. You should only have five percent of those blast cells, but in MDS and in advanced forms of MDS or leukemia then you have many more. Does that make sense?

Q1: Oh, it makes perfect sense. I have another question relating to that though. I just had a bone marrow biopsy and there was a considerable difference between the number of blasts in the aspirate and in the core. Would you explain the difference to me between the two?

Dr. Christopher Lowrey: Yeah. So, in either case you're just looking a very small proportion of your total bone marrow. So, like I showed on the diagram we have bone marrow in our hips and our sternum, our ribs and you just take this little tiny piece the size of a grain of rice. So, that might not give an accurate depiction of what's happening throughout the whole bone marrow. It was just a little tiny piece and then when we look at the aspirate that's just a small amount of the marrow in a liquid form that we look at. So, it might not correlate. Usually, it's pretty close, but sometimes it doesn't match up. Another reason is that they're often measured in different ways. When we look at blasts in the liquid part of the marrow what the pathologist does is stain them and they just count. They count usually 200 cells and say what the percentage is. When they look at the actual what we call the core, it's much bigger and they use different stains. So, different cells can stand out. So, there can be slight differences and we as your doctors we try and integrate that in our mind to come up with kind of average what fits the best

Q1: Thank you.

Dr. Christopher Lowrey: You're welcome. That's a pretty complicated question. Pretty sophisticated. Yes?

Q2: Are there any percentages or statistics in terms of MDS in patients progressing full blown leukemia?

Dr. Christopher Lowrey: So, the question is are there statistics about progression from MDS to leukemia and actually Dr. Hill is going to tell you about how we think about that, but there are certain characteristics in a given patient's Myelodysplastic Syndrome based on the biopsy, based on their blood counts, based on the blast count that help us predict who is more likely to progress to leukemia. Thousands of patients have been studied to come up with what we call a model, a predictive model and using those characteristics we can tell a new MDS patient what their chances are of progressing to leukemia. Dr. Hill will talk a little bit more about that.

Any others? Yes?

Q3: You mentioned radiation as possible cause of development of the cells. Does this include the normal radiation that has to do with dentistry and other tests… testing where radiation is normally used?

Dr. Christopher Lowrey: So, probably statistically there's a tiny chance that that might give a person MDS, but what we're really talking about is people have like job exposure to radiation or the people who are… like your Chernobyl. The have a higher risk of leukemia and MDS. Things like that are what we're really talking about. I wouldn't worry about going to the dentist or things like that.

Q3: I thought not.

Dr. Christopher Lowrey: But that's a good question. I'm sure a lot of people have that question. Anything else? Yes.

Dr. Kenneth Meehan: So as part of the registration process, questions were submitted also. So, there were two questions in particular for you, Chris, and the first question is, "I was recently diagnosed with MDS. Is there an increased risk for my daughter to develop MDS?"

Dr. Christopher Lowrey: Oh, great question. I'm sorry. I probably should have put that in my lecture. So, MDS is not genetic. It's not passed on in families. So, a son or daughter can't inherit from a parent and that's really important to know. The only time where it might be an issue if they had the same exposures like through a toxin or to radiation or something like that, but you don't pass it on. That's really good to know.

Dr. Kenneth Meehan: And another question that might be pertinent more to Dr. Hill, but you could address it also is, "So, at the time of diagnosis the DNA analysis is critical. How does this impact treatment or prognosis?"

Dr. Christopher Lowrey: Yeah. So I didn't go into a lot of detail about it because like Ken said Dr. Hill will, but we actually can look at the mutations in the DNA and we do that in different ways. We can look at the chromosomes. That's called the karyotype and certain breaks or rearrangements in the chromosomes predict because we have data on thousands of patients predict how people are going to do if they're likely to progress or not progress, for example, and more recently we can actually sequence individual genes that we know lead to MDS and certain of those genes can predict a better or poorer prognosis and I think in the future we're going to be able to look at those genes that are mutated and pick the best treatments based on those mutations. We don't really have that much yet today, but I think that's coming really soon.

One more? Yeah.

Q4: Is there a median age for survival once a person is diagnosed with MDS or does it depend upon the type?

Dr. Christopher Lowrey: It depends upon the type and those prognostic indexes. So, the question was once somebody gets MDS what is the prognosis and that's what the score is that Dr. Hill's going to tell you about. MDS can vary dramatically from months to over 10 years and that's one thing that makes it kind of difficult to deal with, but we can provide some guidance based on the characteristics of the MDS.

Dr. Kenneth Meehan: I'd like to thank Dr. Lowery. From a treating standpoint, it's difficult for us to talk with you about MDS because it's not just one disease. It's not a lung cancer. It's not breast cancer. It's a spectrum of diseases and I think… (Inaudible 27:21) So, it's a spectrum of diseases and sometimes there is patients will have MDS manifesting just as a low red count. The white count, the platelets will be normal. Sometimes they'll present just with a low platelet count. So, Chris did a really nice job to show you how it could affect any sort of cell line. We'll move ahead now to Dr. Hill and Dr. Hill will talk with you in more detail what are some of the treatment options available for MDS. So, Dr. Hill performs his specialty training at the National Naval Medical Center in Bethesda as well as the National Cancer Institute and he's currently the director of the Allogeneic Bone Marrow Transplant Program. So, Dr. Hill…

(Applause)