

Speakers

Christopher Cogle, MD

Leslie Pettiford, RN, BSN, CCRC

Christopher Cogle, MD: This is a patient and family forum. I first off wanted to thank the MDS Foundation for sponsoring this event and for organizing it, for bringing everyone here together today and also to our pharmaceutical sponsors who are joining us on the side table for their support of the MDS Foundation. My name is Chris Cogle and I'm a specialist in blood and bone marrow. I specialize in MDS and leukemia. I do not only clinical work, but I also do laboratory work where we develop new drugs for patients with MDS and leukemia and so it's with great excitement that I get to come and speak to you today about some of the major advances that we've learned about MDS and also to give you a clue into what's going on inside your doctors' heads when they're sitting down with you to talk to you about what's going on with your blood and bone marrow. I also have Leslie Pettiford who is here with us today who will be a co-presenter and she is a leukemia and MDS research nurse, research coordinator, and she's being doing nursing for close to 15 years and several of those years she has done research coordination for several of our clinical trials. So thank you very much for Leslie for being here. You'll speak later.

So, what I'd like to do is to start off the conference talking about what is MDS. To start off from that perspective from biology and so if we look at what MDS is, let's start off with the Myelodysplastic Syndrome and so it's actually... it's a Greek word and if you tear apart that Greek word what it means... myelo means bone marrow, dysplastic essentially means funny looking and syndrome means a group of symptoms. So if you put together the term Myelodysplastic Syndromes it's a group of funny looking bone marrow. That's essentially what we're saying when your doctors are saying it. We just put a Greek word on it and we make it sound more scientific. That's what we're doing.

So, there are four major concepts that I want to talk to you about MDS and on this first concept the title that I have for this is the Picasso Premise. So, let's start off with Picasso. Now as many of you know when you approach a Picasso or modern art painting, it's very difficult just to walk up to it and appreciate its brilliance. Now for those of you that can appreciate the brilliance of Picasso, it's usually because you are able to draw upon your experience of looking at what a normal object is. So in this case, Picasso is showing you his guitar on his table and I'm showing you my guitar on my table and to appreciate the brilliance of Picasso or his derangement depending on what was going on in his mind, you can see where he put the fret, the sound hole. You can see where he put the screws for tuning and you can see... you can begin to appreciate what's really going on in Picasso's art. Well in a very similar way, we are doing that with MDS and so to understand MDS, your doctors need to understand what normal bone marrow is. So if you want to understand MDS, you need to understand what normal bone marrow is and so we start from there and so what you can see here in this slide are a bunch of bone marrow cells and the dark purple are the nuclei. That's where the DNA is and that's what codes for when a cell wakes up, goes to sleep, turns into a red cell, turns into a platelet cell, that kind of thing and in the bluish part outside of the nucleus is called the cytoplasm and that's what we doctors look at to figure out what's a red cell, what's a white cell, what's a platelet.

Now in the situation of MDS, you can see it's a very different picture. So first of all, you've got a bunch of... a lot more of these purplish circles. So, there's more of these cells. That's unusual and the other thing is that some of the purple nuclei are odd shaped. There's some of them that are shaped like a figure 8. There's some of them that are kind of twisted. They're not all round and so that's funny to a doctor as opposed to what's normal. So we say 'funny looking' it's that over there at the right side. That's the MDS. So, I hope that you when you're sitting there you can appreciate that's difficult. I mean, it's hard enough to figure out what's funny looking or what's funny from person to person, but when you look at a microscope slide that's pretty nuanced to figure out what's funny looking. Well, that's my feeling as well and so my... So I and my group, we questioned whether or not MDS was being accurately diagnosed. So, there's many of you here today that have the diagnosis of MDS and according to our state cancer registry, MDS is an extremely rare diagnosis. So based on their predictions, it should only be a handful of people in this room, but we have close to 50 people in this room and my group believes it's because we are missing... that the Cancer Registry is missing cases of MDS. So to test that what we did we went... we talked to the University of Miami which is where the Cancer Registry is and we asked them how are you diagnosing MDS? How are you picking this up? And what they told us is that they take these paper charts. They get all the paper charts from around the state get sent down to Miami and then they calculate based off of population. So based off of their count, only around 3 people out of 100,000 in the State of Florida have MDS. That seems kind of low. So, what we decided to do is we asked them, "Well, do you have a better method than paper?" I mean, we're in the 21st century and they said, "It turns out we do. We have electronic files sent from every bone marrow done on any patient in the State of Florida. The electronic files get sent to us in Miami." So, we asked them, "Well, why aren't you looking at that?" and they said basically because we don't have enough money and person power to be able to look at all these electronic files. So, we got a grant from UF Shands Hospital and from Moffitt Cancer Center and we looked at the electronic files and when we do that what we find is that the incidence is actually almost double of... than what's estimated by the Cancer Registry if you use the electronic format. Now if you look at individuals that are 65 and older which is most of the people in this audience, what you find is that it's not 20 out of 100,000, it's actually 75 out of 100,000 people in the State of Florida have MDS and I have to say we probably missed cases even using the electronic format. So, my point here with this is that when we dig deep and use, I think a more accurate and precise method for capturing MDS, it's much more common than what we currently think and so we've been talking to policy makers in Tallahassee and throughout the state to provide for more resources for patients with MDS to help with anemia and the low platelets and the risk for infection.

The second concept that I want to talk with you about and that concept is called clone wars and so this is something that we've learned over the past year. So, I mentioned to you when we look at a bone marrow of a patient with MDS and here in arrows you can see in this situation we have early grandfather red cells that are going to eventually make tiny red blood cells that float into the bloodstream of this patient, but around... so and the cells that have arrows on them you can see, I hope that you can see that there's some blue dots that are hovering around the nucleus. Those blue dots are iron deposition. They're clumps of iron and the problem with these early red cells is that they're not able to take the iron, wrap it in that hemoglobin protein and package it in the red cell. So, this iron gets built up and it clogs up that early red cell. This is a form of MDS called refractory anemia with ring sideroblasts. So if your physician that tells you that you have a

ring sideroblast this is what that cell looks like and this you can see often in MDS. You can see it in some other conditions, but MDS is one of the hallmarks.

How do we diagnosis this? So, we use the light microscope. My point with the light microscope is that this is an old invention. It was invented back in the 1600s. So, we are using 500 year old technology as the cornerstone for diagnosing MDS, but also following MDS. So if that troubles you, I agree with you. We need to have better technologies and so that better technology gets at... we need to go on the inside of the nucleus. This is that... usually it's purple colored, but in this case it's sort of a dark reddish color. We need to get on the inside of that nucleus and we need to look at the chromosomes in the genes on the inside of that.

So to get into chromosomes and genes, let me tell you what we do. So, what we do is we take the MDS cells, we put them in a dish, we let them divide and then we take a picture of those MDS cells right as their chromosomes are being organized and split across 2 different cells and so here you can see the chromosomes on the inside of MDS cell and what we do is we use a computer to take pictures of each of the chromosomes and then the computer matches up each of the chromosomes. So, you got 23 of your chromosomes from your mom and 23 from your dad and so what we do is the computer matches up the pairs of the 23 pairs. Now, the job of the chromosome expert that works with your doctor is to figure out where do we have a situation that one chromosome doesn't match the other chromosome and that is what's called cytogenetics. Again, we use a light microscope and a computer to do this. So, it's older technology, but it was only developed back in the 1960s and '70s. So, even though it's older technology, it's still relatively new. Now and to let you know the difficulty is sort of like do you remember those *Highlights* magazines where you had to compare 1 picture to the other and find out what's missing in it? That's basically the level of matching that it takes for this.

So we're now going to dive deeper into the chromosome and so for me to take you deeper into the chromosome, I may need to give you a refresher course on what a chromosome is and what the genes are and the DNA is below because many of you have not taken biology course where you talked about DNA and if you have it was probably with fruit flies and eye color, something from a long time ago. So, chromosomes are basically wound up DNA, DNA and proteins, and so if you look deep on the chromosomes what you have is a coil of the DNA almost like a telephone coil and you can see the here it in the DNA and the proteins in green. You go deeper and deeper and deeper and this green strand that I'm showing you here is the DNA. The little balls are the proteins, the histones. So, the DNA gets wound around that. If many of you in the room remember the old telephones that we used to have that have the coil on it and then it would get so twisted it would be like a big knotted mess. That's exactly what our body does with the DNA. It makes these coils, this coil upon coil of the DNA to in order to package it very tight. So, we have chromosomes that are in chromatid and then we have genes, we have the DNA in the genes that are deep inside the chromosomes. So, that's your Biology 101 lecture.

So now that you understand what normal is, let's go to what's abnormal. So, what we understand about... what we think we know about cancer is that you start off with a normal tissue and you have a genetic mutation, a gene mutation. So, remember that DNA that I showed you. That DNA gets messed up and one mutation, not that bad. A cell can usually recover from that, but if you get two mutations, that could be bad and if you get three mutations, if you get this accumulation

of mutations what ends up happening is that cell starts to grow out of control. It also depends on what actually is being mutated. So, this idea of a normal tissue having one mutation, two mutations, three mutations accumulation, this is called the multi hit hypothesis. Multiple hits. Hits to the genes is what it's referring to. So, this was conceived around the 1970s and has really dominated our understanding of cancer ever since. So, your blood and cancer doctors think about your MDS as one cell that has at least one gene mutation, possibly two. That is the current thinking of most doctors about MDS and it turns out we're wrong. We're very wrong actually. So this is some of the recent research that's come out and this is now more towards research questions we have now Terada (sp?15:42) and his graduated student, June, here in the lab. They're researchers here at UF and so now that I caught you up to speed to where Dr. Terada is and his understanding of genetics, I can talk to you about where we are with MDS and leukemia.

So, we are now using not the light microscope. We are now using a way to sequence the genes of your MDS cells, your leukemia cells and so we can read every single letter of your MDS cell and by doing that what we can do is we can track what your MDS cell has as far as gene mutations. The other thing we can do with this technology is that we're finding out that it's not one MDS cell. It's actually multiple MDS cells that we have and so as you can see here we start off in this particular patient the green is a normal blood stem cell and in this MDS patient only about a quarter of this patient's bone marrow, only a quarter of it was normal. Then we have two different MDS clones, an orange clone here and yellow clone. Over time this patient was not treated for their MDS and over time this particular patient developed leukemia and what you can see here is that the MDS clones gave rise to daughter clones which gave rise to a granddaughter clone which gave rise to a great-granddaughter clone. So and then eventually and this is when those clones eventually spilled into the bloodstream and that's when it became a leukemia. So, this is our new understanding of MDS is that it's not just one cell we're treating. It's not one disease inside our patients. It's actually multiple MDS clones on the inside of our patient. So if you're sitting here and you're thinking, "Well, I've got multiple MDSs, what happens when I get treatment?" So, here's a case where... So, this is actually a leukemia case. This is where a patient developed... had MDS, developed into leukemia. We used this brand new technique of being able to read every single letter on the inside of the DNA of the MDS cells. This is called whole genome sequencing. When we use this brand new technique what we find here is we have, again, multiple clones. In this case, we've got a purple, a yellow and an orange clone. The orange, by the way, is a daughter clone of the yellow clone. So, we already are starting to have some daughter and granddaughter action happening. When we gave chemotherapy to this patient, look what happens to the clones. Most of them go away. In fact the purple clone goes away completely, but deep inside this particular patient, we still have a residual clone, a microscopic level. It was actually at a level below the detection that we could tell from using a light microscope and so over time treatment was stopped and over time that clone woke up and gave rise to a great-granddaughter clone here in red that was now resistant to the chemotherapy from before. So, this is a brand new understanding of MDS and leukemia and what I look at as clone wars. So when I approach my MDS patients, my patients with MDS or leukemia, I don't think of them as having only one disease. I think of them as having several MDS inside of them and what we need to do the first thing that we need to do is find out what are the chromosome and genetic problems on the inside of those MDS cells to help us figure out what kind of treatment we should give first and then how to follow that MDS after treatment to make sure that it's gone and to keep it away.

So if you were to say I want to sign up and I want you to sequence my MDS, right now if we were to go here at the University of Florida, it would only be in the research lab that we would do this and Dr. Terada, the quote that I got for us to do it on a patient is around \$10,- to \$15,000 using all our core lab facility. Now, Dr. Terada knows and I know that the price is coming down dramatically as our computer technology is getting better and I would certainly love to hear from Dr. Terada's in the audience about if there are less expensive ways that are out there that we could do this because in the coming years, our goal is to be able to sequence the entire DNA of the MDS cells so we understand them better.

The third concept I want to talk about is parenting and absentee parenting. So to start off, so here I am with my two sons and I'm a new parent. I have to tell you that I'm learning a lot as many of you have. One thing I learned is that safety locks are not a barrier for a kid, especially little toddlers with little mischievous fingers. They can get through a lock within a matter of seconds and what I've learned is that the best thing to keep your kids safe is just being in the room and watching them and you can prevent so many catastrophes... I had so much faith in these locks that they don't work. So, that same kind of parenting turns out to be very true actually in MDS. So, there's a parallel there.

So, I'm showing you a bone and the bone marrow. Now, a lot of us have thought about bone as just a hard bucket that contains all of our blood stem cells in our blood, but that bone is not just a bucket. It's actually more than that. It's actually a living organ that helps talk to our blood stem cells and so let's talk about... let's go back to normal before I talk to you about abnormal. Before I show you the Picasso version, let me show you what the normal version is. So a hematopoietic stem cell, a blood stem cell, has the capacity to self renew. It also can create multiple types of blood which you know as platelets, white cells and red cells. You've known that. These are the two hallmark features of stem cells. That's what they're meant to do. Now, the other thing that the stem cell can do is that it can go to sleep. So, the question is where in the bone marrow does all of this happen and that's a very active area of research. So, what we know and what we're studying and so this is work from Ed Scott who's a PhD scientist across the street is a blood stem cell expert. He has developed a model to look on the inside of the bone marrow and track where do blood stem cells like to sleep, where do they wake up, where do they produce all the white cells and red cells and where do they go back to sleep because if we can find out where they do that then we could possibly design treatments that would, for example, make the stem cell wake up if your blood counts are too low and push your body to make its own red cells. So, in the yellow arrows here on the right what Dr. Scott has found is that blood stem cells love to sit on the lining of the bone. So, there's something on the bone lining that is sticky or that keeps these blood stem cells in a quiet state. So, if this is the situation and I'm going to show you here in a diagram where the blood stem cell sticks to the side of the bone and that's where it does its self renewal. Where we think that the blood stem cell wakes up and starts producing red cells is out around the blood vessels in the central part of the bone marrow and where does it fall asleep? So far, Dr. Scott's evidence shows that it goes to sleep back along the bone lining. So, I hope that you're so far impressed that that the bone is instructive and there's some possible... some parenting going on and it turns out that that's true. So, Dr.... There's a physician scientist up in Boston named Dave Skadden who did a really interesting experiment and said, "Okay. If the bone is so important, what if we got rid of a lot of the cells that are embedded within the inside

of the bone?” and so he genetically engineered a mouse that had a... that was not able to have a lot of the cells inside the bone. So, he essentially got rid of all the parents and so let's see what happens with the children. So, you let the children lose and what ends up happening is that the blood stem cells ended up showing an MDS type of growth, a dysplastic growth, and if you gave those dysplastic cells enough time without parents what they ended up developing was into a leukemia. So, what we've learned is that if you take away the parenting cells on the inside of the bone, the blood stem cells, they grow out of control and they form this MDS type picture which eventually leads into a leukemia. So, what this means to us is this actually speaks to the origin of MDS. So for many decades, we really focused on the blood stem cell as the origin of MDS. It turns out that it may be the bone and so what we ought to do is look at what's the damage to the stroma or the environment or the scaffolding on the inside of the bone marrow not just on the inside of the blood stem cell.

So my fourth and final concept that I want you to understand about MDS before we go on is called sanctuary. So, where do these MDS cells live? So, research that my lab has done is asked this question and what we find is that these cancerous blood stem cells they jump out of the bone marrow and we have evidence that they actually can turn into blood vessel cells. They also hang out around the blood vessels because the blood vessels give them growth factors. So, blood vessels aren't just pipes that shuttle blood from one place to another. The blood vessels are actually organs almost like endocrine organs and these hoses, the blood vessel hoses, actually secrete growth factors around them that help protect the leukemia cell and so these leukemia cells what we found is that some of them can turn into blood vessels and when we give chemotherapy what ends up happening is that it gets rid of those cancerous blood cells out of the bone marrow. The chemotherapy is washed out, but there are still these leukemic or cancerous blood vessel cells that are hanging around and we have evidence that they can actually pop back out into a leukemic or cancer form which can go to the bone marrow and can repopulate the bone marrow and so this is obviously very concerning and it may be the answer as to why MDS and why leukemia can come back at a later point in time and it's not just that resistant clone, but that it may be that they're hanging around blood vessels. So, we've done research that has also found that the MDS cell is also not just a blood cell, but it actually shares some proteins on its surface that looks very much like a blood vessel. So, MDS cells are very crafty. They're not just blood, but they also look like a blood vessel. We think that gives them a protective advantage. They're very crafty cells and so what we've done is we have targeted that blood vessel layer down below and we've asked the question if we get rid of that blood vessel layer can we starve that MDS and leukemia cell and so we found that we can and we can do it with a drug that was developed from... or found in the South African bush willow. There's a bark of this plant that has anticancer properties. So back in the 1970s was when it was discovered in South Africa. Our federal government sent scientists over to Africa to find out new plant that could kill cancer and so there is this group that went to Africa and they heard from the Zulu tribe that the Zulu tribe would use the bark of this tree to fight cancer. Well, it turns out that the bark of this tree has a compound in it that kills blood vessels that support cancer. So, that research was shelved back in the 1980s and about six or seven years ago my lab came across this compound and thought that it could possibly work in the situation of MDS and leukemia. So, we pulled it off the shelf. We tested it in the lab. We tested it with some animals that had MDS and leukemia and we found that it worked. So, we wrote a critical trial protocol, the FDA approved it and we have now treated actually a total of nine patients on this drug. We've done an escalation trial with this

drug. Leslie Pettiford is the research nurse on this trial and she'll talk to you about what a clinical trial is later on today, but so far we've treated nine patients. Two patients have responded to the drug so far and we're continuing to increase the dose of the drug to see if we can get more people that are going to respond to this.

So, I'm going to stop there. I've given you a lot of information and we're going to enter into a question and answer period, but before I do I want to thank several of our sponsors that have sponsored all of this research. The MDS Foundation, the University of Florida and Shands Hospital as well as the Leukemia and Lymphoma Society and so with that, I want to thank you for your attention and so we'll take some questions about the presentation if you like.

Q1: What was the name of the drug that this plant (inaudible 32:00).

Christopher Cogle, MD: The question was what was the name of the drug. Right now, the drug is called OXi4503. Yes. It doesn't have a catchy name yet, but it's still in the testing phase. Yes, ma'am?

Q2: Is the presence of normal (inaudible 32:20) and a positive prognosis (inaudible 32:23)?

Christopher Cogle, MD: So, the question is when the chromosome test comes back normal, is that positive? What does that say to prognosis? So, I'm going to put air quotes around 'normal' as the first point because...

Q2: (inaudible 32:41)

Christopher Cogle, MD: Exactly. So, the point is that the technology using a light microscope says that it's 'normal'. The issue that we have is that the technology is not sensitive enough to detect the mutations at the gene level. So about 40 to 50 percent of patients with MDS have 'normal' chromosome results, but we know that if you dig deep enough using a higher sensitivity of technology, there are multiple gene mutations. So your question... the next part of your question then is what do you do with a 'normal' uninformative, insensitive test result and right now we put the risk of 'normal' in an intermediate risk which is not helpful. Right? Because it would be helpful to know if this is going to be aggressive or if this going to be something responsive to treatment. So right now, we put normal in this middle group where we don't really know yet. Yes? Can you want to follow up on that question? Yes.

Q2: The fact that you mentioned (inaudible 33:53) does the presence of osteoporosis have any fit in this then?

Christopher Cogle, MD: That's a great question. So, the question was does osteoporosis in some way relate to MDS? You know, we don't know. It's actually a really good question. I mean, osteoporosis is a breakdown of the bone. The thought is that there's not enough bone being put down to keep up with the bone loss and the thought is that it's the osteoblast cell that helps make the new bone. So if you take away osteoblast, could that relate to MDS? That's a great scientific question. I have never seen any link. I've never seen these studies, but that's a wonderful... It would be a wonderful research project. Yes, sir?

Q3: I wanted to ask you can you tell me how many misdiagnosis there are for MDS in Florida.

Christopher Cogle, MD: So, the question is how many times are there misdiagnosis of MDS. I can't answer that exact. I can answer to you how many uncaptured cases there are according to the Cancer Registry and what we think is approximately three out of four MDS cases are not captured by the Cancer Registry, which is a lot and some of the reason of why that's not captured is because a lot of times doctors don't feel very confident that they could label a person with the MDS diagnosis just based off of a bone marrow biopsy. That's probably the more common case even though the patient seems to have MDS clinically. So, it's very difficult. Yes, sir.

Q3: What I mean is though like if a doctor says to a patient you have MDS and then they don't, they are misdiagnosing as that other thing and it sounds like it. It's the same symptoms.

Christopher Cogle, MD: I got you. So, the question is if a patient was being told that they had MDS when they could have actually something else. In my experience which is a skewed perspective, I agree because I usually only see cases of MDS or questionable MDS. I have undiagnosed probably about 6 to 12 patients in my career.

Q3: And that's several hundred out of...

Christopher Cogle, MD: Out of several hundred. Yes. Several hundred. Probably close to 1,000 patients. About 6 or so, I'd say, and instead of MDS it was actually like an iron deficiency or a vitamin deficiency or most often alcohol abuse because alcohol abuse can really... can put a heavy stress on the bone marrow. Sometimes there can be the combination of alcohol abuse, iron deficiency, B12 deficiency and MDS all in the same patient and so what we end up having to do is have the patient stop alcohol. We give them iron. We give them B12 and folate and then we have them come back and if they still have low blood counts and a funny looking bone marrow then we call... then we say okay there was MDS there, but that can take a long time for all of that to happen. So, it is difficult. Yes, ma'am?

Q4: I know that at some point there's a split from the MDS and then those who are going to have the potential of leukemia but this group over here. Did all the slides that you show, did they apply to both branches?

Christopher Cogle, MD: Yes, they do. So, I agree with... So, the question is MDS can present in roughly two ways. One as a leukemia form of MDS and the other which is what we could... I would call a bone marrow failure form of MDS where the patient doesn't develop leukemia. Just has a bone marrow that's just not maturing properly and it's making all these funny looking cells. So as far as... So, yes. A lot of the slides that I presented especially the bone cells that can form both the bone marrow failure type of MDS and then over time develop into a leukemia form. Now, the slides that I presented where there are multiple clones that develop granddaughter, great-granddaughter, great-great-granddaughter clones, that was mostly in a leukemic form of MDS, but it is really called the question about the bone marrow failure MDS patients where we should go back and really look at their bone marrow and count how many

clones that they have on the inside of their bone marrow. It's a spectrum and it's connected. Yes, sir.

Q5: I'd like to ask about (inaudible 39:01) as compared to the light microscope and it seems like it's a little bit better over time and how is it actually used now?

Christopher Cogle, MD: Great question. So, his question was on the technology part of the presentation. The difference between PCR which stands for preliminary chain reaction. What that does is that allows us to look at the DNA level compared to the light microscope. What's the better technology? How do we use it? The problem with PCR which is that's how we look at the DNA and the genes. The problem with that is that you have to know right now, you have to know what genes you're interested in. Now, there are 23,000 plus genes on the inside of your cells. So out of those thousands and thousands of genes, how do you know where to direct the PCR? That's been the major obstacle over the last 10 or 20 years. Where we are moving to is using PCR in a different way to sequence, to read every single letter of every single gene. So, there's a way to use the PCR tool, but use it instead of looking for... So, as a parallel. So instead of... So if you have a novel, *War and Peace*, okay, and I give you this novel. Instead of using your eyes to look at words and having if I were to say, I want you to find every time they use the word 'nonetheless' on the inside of this novel. It's very difficult. You'd have to know where that word might appear, but if you use your eyes to read every single letter, it may not make sense of you to read n-o-n-e-t-h-e-l-e-s-s. It may not make sense to you to read it that way, but if you use your eyes to read it like that and then after the fact put it together in a computer that technique would be called genome sequencing where you read every letter and then after the fact you put it all together with a computer and figure out where those genes are. That application of PCR is only about 10 years old and that is a very unbiased way of looking at the genes. So the problem with PCR in the past is that it took some bias to figure out where you wanted to look. Nowadays with the way we're using the technology, you don't have to know where you want to look. You can just sequence the entire genome. The benefit of light microscope is that you can look at a bunch of cells all at once. You don't have to be biased and so that's why a light microscope has been our major tool. It's because you can just look and see the cells. The new technology has taken awhile for us to figure out how to use it and combine it with a computer to be a more powerful tool. Are you okay with that answer?

Q5: Yeah. It's a great start.

Christopher Cogle, MD: A good start. Okay.

Q6: I'm just wondering when you're going between, let's say MDS and your AML, how you prime your test (inaudible 42:42) bone marrow. They say it's about the same. Make it when you want to use it.

Christopher Cogle, MD: Right. So, how you... So, the way we follow along now is that on... leukemia patients and MDS patients we sometimes send out of the 23,000 genes we will sometimes send for gene mutations on only 2 out of the 23,000 genes. One of the genes is called FLT3 and the other one nucleophosmin 1, NPM1. We'll follow for those 2.

Q6: (inaudible 43:18).

Christopher Cogle, MD: Well, sometimes we'll send for the CEBPA, the core binding factor protein alpha. Sometimes we'll send for that. That's mostly in leukemia though not so much in MDS. It still needs to be validated in MDS. So, my point is that we're only talking about 1 gene, 2 genes, 3 genes out of the 23,000 plus. So eventually, we'll move to looking at all of the DNA, but for now we're looking at these genes. Not only... We don't know what they mean as far as diagnosis. Now in leukemia, I can give you a diagnosis, but in MDS we don't know what the significance of having a nucleophosmin gene mutation is. We don't know. In leukemia that would be a good thing because if you have this mutation, there's a potential that we could cure you with chemotherapy. In MDS, we're not sure yet. We don't have those studies completed yet. Yes.

Q7: What does it mean when your bone marrow biopsy shows blasts, but the blood work continues to be good? Can that go on or...?

Christopher Cogle, MD: Yes. So, the question is if the bone marrow shows blasts after treatment and the peripheral blood is showing a response. What does this mean and should you keep going? And we'll get into that when I talk about some... the treatment and follow up in the next presentation, but that is a good thing. So, that is a... It's what we call a hematologic improvement and we would continue to go forward because our major goal is to stop the transfusions. Stop the need for transfusions. We would, of course, want to repeat that bone marrow biopsy to make sure that those blasts, those early cancer stem cells, are not growing out of control and so we would definitely want to go forward, but we would go forward cautiously. Yes, you've been waiting awhile.

Q8: I just recently (inaudible 45:18) six months prior to that I had irregular heartbeat (inaudible 45:29) now I'm on coumadin however my problem are low platelets. So, the two are going to work against each other and the cardiologist has recommended that if I qualify for (inaudible 45:45) procedure on my heart. Is there anything that I could do to get off of coumadin without having to go through this procedure? In my circumstance, what is the timeframe that I should go back and have my platelets... my blood work checked?

Christopher Cogle, MD: All great questions. So, Marilyn is asking so in her particular case what she's saying is that she has an irregular heartbeat which it sounds like atrial fibrillation is what... so atrial fibrillation and also diagnosed with MDS with low platelets. So, let me... So, it's a complicated... It's certainly a very complicated and I would... I usually spend an hour with my patients going over the full medical history and the medications, etc. to get the exact answer, but your main question is what could I do to get off of coumadin because atrial fibrillation has the chance of me developing a clot in my heart that could go to my brain? So, could I get off of coumadin in order to lower my risk of bleeding because of low platelets? That's really a cardiology type question and part of it... So, I would work with a cardiologist to try to figure out if your atrial fibrillation could be related to a possible anemia. So Marilyn, do you have an anemia? A low red cell count?

Q8: (inaudible 47:26) I don't think so.

Christopher Cogle, MD: Okay. Because sometimes people develop atrial fibrillation. So, the fluttering of the heart because there's not enough oxygen carrying cells running through their body. So, that would be the first thing that I want to check is that is this because of an anemia. If it is because of an anemia, then let's fix the anemia first and then see if your heart will go back into a normal sinus rhythm.

Q8: I only had that once and after that point my blood pressure was fine and actually I don't know if was caused by stress or what, but it was a one-time thing, but they put me on coumadin.

Christopher Cogle, MD: So, I would need to... So if I was your physician, I would need to talk with your cardiologist about was it a one-time atrial fibrillation and are you now in a normal sinus rhythm because there's different recommendations on coumadin depending on the heart rhythm, depending on the blood counts, things like that. The other thing is we as some of the people in the room know just because you're on coumadin doesn't mean we can't start treatment with you and so we have lots of patients that are on blood thinners and on a drug like Vidaza or Decitabine or Revlimid. So, we can treat patients that are coumadin. I think what you're... I think the concern in your voice is very appropriate because it does... We would need to watch your blood counts very closely. We would not need to watch your INR and things like that to make sure the coumadin level is right. Thank you for your question. Yes, ma'am.

Q9: (inaudible 49:06) a diagnosis between men and women like did more men get it or women get it?

Christopher Cogle, MD: The question is is there a difference between sex, so male versus female and yes. So, if you were to go to the Cancer Registry and ask who gets it more, men or women, they would say that it's actually older white men are the... is the most common group that has MDS or the highest incidence. However, when my group looked at those missed cases of MDS, it was actually younger women that were missed by the Cancer Registry and I'll tell you there's a part of me that questions whether doctors who are doing bone marrow biopsies on people and they get a young woman in and the bone marrow looks like MDS and the peripheral blood counts are low and they think, "Oh, but this person's not an older white man, so it's probably not MDS." I wonder... We have no proof of that, but I wonder if some of that bias could be going on in some physicians' minds, but the missed cases of MDS were younger women and that's a point to make. Yes, Nancy.

Q10: Do I understand correctly with this (inaudible 50:25) the clones, for instance a P and H clone and is a child or a grandchild or whatever of MDS not a separate disease or...?

Christopher Cogle, MD: Okay. So, the question is so if you have a granddaughter clone or a great-granddaughter clone and let's say one of these granddaughter clones develops resistance or... Sorry, not resistance, but an inability to withstand an immune attack and gets hit by the immune system and what that situation's called PNH. So when your red cells and your white cells when they get attacked and they can't avoid the immune system that's called PNH. That can happen in about 30 percent of patients with MDS. That manifestation in that great-granddaughter clone is not considered a... is not usually considered a separate disease because that great-

granddaughter clone if she becomes the dominate clone then... and you still had low counts and the PNH going on, that is the disease and so just because the clone is small in number, it's not considered a separate disease. It's all considered still 1 big collection of clones that are all vying for dominance. That's how we view it now. Yes.

Q11: My husband was diagnosed with MDS after a heart attack (inaudible 52:11) that atrial fibrillation and I have another friend who after hip replacement. I wonder just is there ever a connection with the trauma to the body that MDS rears its ugly head sometimes?

Christopher Cogle, MD: Yeah. The question is a relation between trauma to the body and MDS. There's not a direct correlation that we've seen. However, the correlation that we have seen is that oftentimes as the first time that somebody comes in and actually gets a blood count and that's when it's detected. So, it's more of a coincidence than anything else. Yes.

Q12: (inaudible 52:47) called IBG and I'm wondering when I first took it, it would jump way up to 8 on my immune system and now it's staying at 3 and then he gives me a shot of B12. When I come home, but one day I'm worse... I feel worse than ever and my immune system will not come up and I'm taking this drug once a month and I think it's making me worse, but he says he thinks I have MDS and won't do nothing about it.

Christopher Cogle, MD: So, the question is that... Christine is getting IVIG and she's saying and as well as B12 and folate and it sounds like your counts are still low. So, I guess the question I would pull out from that is that we can use immune suppression as a form of treating MDS, but we usually use... we usually modify immunity in people that are younger than 60 years old. That's where it seems to be most effective. There are some other situations like if you have a PNH clone, an (inaudible 53:59) which is somewhat of an autoimmune condition. That's where we would do some immune therapy on those patients. I'd be happy to talk with your doctor over the phone as an unofficial thing to talk about your case. I'd be happy to because it sounds a little more complicated than something I can figure out in 30 seconds at the microphone.

Q12: So, I've been taking Neupogen and that wasn't helping and the minute he put me on this it went real up and then it dropped down and it's staying like that and I feel I'm getting worse instead of getting (inaudible 54:35).

Christopher Cogle, MD: Yeah. We should talk. We should talk. You've been waiting awhile. Yes.

Q13: If you've been on Revlimid and then hemoglobin went up and it stayed up for a long period of time. Now, it starts to drop. Is the Revlimid going to be as effective as it was the first time?

Christopher Cogle, MD: So again, the Revlimid... you're on the Revlimid. The counts came up and then the counts went down while on Revlimid or was there a holiday off of it?

Q13: A hiatus off of Revlimid for 14 months and now the hemoglobin's dropping down.

Christopher Cogle, MD: Right. So the question is when you come off of Revlimid, will it work just as good if you go back on, but let me ask you... So, why'd you come off the Revlimid?

Q13: (inaudible 55:30).

Q13a: It did so well.

Christopher Cogle, MD: It did so well and you wanted to get off the drug. You felt better. Okay. In my experience, about 50 percent of people get that good response back again, but it's with caution because even if you do get a good response the times I've seen it is that it's been a little more short lived in that good response. So, you kind of have to be prepared on what to do after as the next step. That's been my practice experience.

Q13a: (inaudible 56:08) AML following through (inaudible 56:10).

Christopher Cogle, MD: No. Are you concerned about leukemia? Not always. Only about 30 percent of people with MDS develop leukemia. So, the majority of people with MDS don't get leukemia. So, no. That would not be my major concern. My major concern would be... Well, I would feel bad for you if you had bone pain, but that would stop my... I mean, my concern would be your low blood counts and keeping you free from infection, from bleeding and making sure that you have enough oxygen carrying cells so that you don't have heart attacks and strokes. So, my main concern in MDS is getting those blood counts up, getting you off... nowhere near transfusions if possible. That's my primary concern and then after that I would be concerned about leukemia progression, but not in everybody. As the question was not all leukemia... not all MDS is the leukemic type. Some are more of a bone marrow failure type. Yes?

Q14: I wanted to know is there any correlation between heavy metals and benzene in the initial cause of MDS?

Christopher Cogle, MD: Okay. So, the question that Donald's bringing up is the link between benzene and heavy metals...

Q14: Arsenic.

Christopher Cogle, MD: And arsenic.

Q14: Arsenic especially. I'm a dentist and that's why I want to know. He has absolutely no statistics on whether dentists get MDS at a greater proportion.

Christopher Cogle, MD: Okay. So, Donald's a dentist and is asking if there's any link that (inaudible 57:44) the ADA, doesn't have any data. Mercury would be another heavy metal, right?

Q14: You know, back in the old days we used to squeeze it (inaudible 57:54).

Christopher Cogle, MD: Amazing. So heavy metals can cause an MDS like reaction in the bone marrow not necessarily MDS, but you can get immaturity and dysplastic changes in the bone marrow and usually if you take away the offending heavy metal, the bone marrow will be able to recover over time. Benzenes absolutely can cause a very permanent and progressive MDS. There is literature and documentation on that, but it depends on the amount of benzene exposure and that's the difficult part to always quantify because everyone's exposed to some benzenes, but the amount that it would take to cause MDS is an industrial amount. You may... I don't know your practice, so you may have been. Yes, sir.

Q15: I was going to ask you about... in other words the complication of for instance the chemotherapy and then that makes your bone marrow weak, it makes your bones weak (inaudible 59:06) and so then you get MDS from that.

Christopher Cogle, MD: Yes.

Q15: Now, how often does that occur? So, is that documented like that?

Christopher Cogle, MD: Yes. It's a great question. So, he's asking so what if you've had chemotherapy or radiation for a different type of cancer and then is there a risk develop MDS. Your answer is absolutely yes. The risk is about between 5 and 10 percent chance of developing a MDS or leukemia, a secondary MDS or leukemia, after having had chemotherapy in the past. Now, we would like to do some studies here trying to find out, for example, in patients that have lymphoma. If we could tell... If we could identify which of these patients would eventually go on to develop MDS, it would be nice to know and we could also modify our treatments to prevent that from developing. So, what we're trying... what we think is happening is that either the bone stroma or the hematopoietic stem cell may have some difficulty in DNA repair. So, being able to recover from that chemotherapy or radiation from before and somehow that leads to an accumulation of mutations. That's what we think may be happening. No data yet.

Q15: No data yet, but the thing is in other words Dr. A is causing Dr. B's treat her for MDS. So, is it that kind of like that, a circle? Can they compensate for that? Can they be like okay, we made this mistake, so we'll correct it?

Christopher Cogle, MD: Oh, I see what you're saying. Yes. So you're saying so if I am seeing patients with MDS because of a past chemotherapy, is there something that I could tell my lymphoma colleagues to do or not do to prevent... so I'd go out of business which would be wonderful. I would love to stay at home with my kids. We do not have enough information about the genes that are messed up because of that chemotherapy for me to be able to go back to Dr. A and say, "Hey, listen, don't give cyclophosphamide," or don't... In this patient that has this genetic susceptibility you might want to lower the amount of busulfan or lower the amount of radiation that you give. We need more research and it's places like the MDS Foundation and the federal government and the Leukemia Lymphoma Society that fund this kind of research which is why it's so important and people like Dr. Terada who do this research that's why this is so important. We don't have the answer yet, but that's how we would do it.

So, let's talk about the more the clinical and treatment aspects of MDS. I'm going to do about 20 to 30 minutes and we'll break for lunch, but we do want to cover this because a lot of the questions or half the questions pertain to the clinical and after lunch we're going to hear from Leslie Pettiford who is one of our research nurses in MDS about clinical trials and also quality of life type issues.

So, the MDS Foundation has many different people involved and it's an international organization. They have a *Building Blocks of Hope* notebook which you picked up today. It's a wonderful resource. We'll also provide the web link for those of you that like to do computer and Leslie Pettiford will go over that as well in her presentation and what we're going to do we've already talked MDS. We're going to talk about how it's diagnosed. So, let me just kind of get into this.

So, what is MDS? Well, I think I've gone over it enough in the previous talk. Now, what happens is that I told you about the funny looking cells. The other name for that is dysplastic. That's another name that your doctors might use. When the cells don't work well or the bone marrow doesn't work, another phrase for that is ineffective hematopoiesis. Again, long Greek words for the bone marrow is done broke. So, what do we do about that? Let me just go through some of these slides that I've given you and go to the diagnosis. So, this is a critical part. So, you get peripheral blood drawn, low blood counts. You have to have a bone marrow biopsy to diagnose MDS and to follow it as well, but it's important that your doctor also tests these additional things like your iron level, your ferritin level. So, ferritin is a protein that carries iron and shuttles it all around your body. So, it's a very important that your doctor tests that. It's important that your doctor to keep track of your B12 and folate levels even though they may not be low in the beginning. It's important that they check it to make sure that your nutrition is kept up to speed. We also will check what's called the EPO level. It stands for erythropoietin. That is a hormone that your kidney produces and communicates to your bone marrow to wake up and make more red cells. Now, another way to get this EPO hormone is to get it via a drug. So, you can get that as an injection as many of you do. There's a long acting version of EPO called Aranesp which you can get IV and a lot of you can get that usually every 2 weeks or so. Now sometimes as we mention, MDS can also have an immune reaction where the immune is overactive and is attacking the red blood cells and they can also attack the white cells, too. That situation is called PNH. It stands for paroxysmal nocturnal hemoglobinuria. Very large collection of Greek words, but it basically means you wake up with dark pee and what the dark pee, well that's the dark urine was was the broken down hemoglobin from the night before. That's how it was known for a century or 2 because doctors didn't have the microscope and all the testing that we have today. So, they went off your urine color, but today we know that it's actually a broken apart red cells that can happen in about 30 percent of patients with MDS and it's important that your doctors think of that during the diagnosis of MDS. It's important that your doctors also consider your thyroid as being a part of MDS. So if you have a low thyroid function that can cause funny looking bone marrow cells and so it would be important for your doctor to first to make sure they... that doctor treats your thyroid and then look at your bone marrow or your blood and see if it's responding appropriately. Lowest testosterone could also lower blood production and so that is a test that we sometimes test and, of course, looking at your kidney function and your liver function. If you have any abnormalities in kidney and livers that can impact upon your bone marrow function.

So, my point with that last slide is that it takes many different testings way before your doctor considers an MDS diagnosis. So, I've seen situations where patients have been under evaluation for 1 to 2 years trying to figure out what's the cause for the low count, the low blood count, and then we finally get a bone marrow biopsy to figure out that it's MDS. So once you get to the point where we think this a funny looking MDS, the pathologists have to convince us that at least 10 percent of the bone marrow has funny looking cells. Ten percent or greater. That's the definition of MDS. We can then risk stratify or we can then try to classify the MDS into 1 of these classification schemes. Now, you can see... So in each of the rows is a different classification scheme. There's the FAB which stands for French/American/British. There's the WHO, which stands for World Health Organization. Then the WHO did it again back in 2008 and there's different types of dysplasia and there's different amounts of blasts. So whenever you see this many types of classification schemes, you can tell that our technology is evolving very rapidly and our doctors can't agree and we're trying to figure out what is the minimum number of types of MDS that there are and in fact there's a recent push to reclassify MDS completely change the term MDS into MDN, myelodysplastic neoplasm to fully appreciate that this is not just a syndrome, not just a low blood count, but this is an abnormal growth, it's a cancerous growth of clones of cells on the inside of the bone marrow. So, you're going to see many more columns happening that's going to extend this slide much longer.

So, what's more important than classifying, we believe, is giving a prognosis. So if you were told that you have MDS, it's important to know how aggressive is this disease and do I have 1 year, 2 years, 3 years or more or do I have less than that because it impacts upon our estate planning. It impacts upon how we spend our time with our career, our job, etc. and so what we've developed is a prognostic scoring system and there's really... there are 3 basic things that we look at. We look at the amount of blasts in the bone marrow, that's number 1. We look at the chromosome problems in those MDS cells. That's the cytogenetics and number 3, we look at how low the blood counts are and how many of the blood counts are low. So, those are the 3 absolute things that have to be looked at when your doctor visits with you and when you do that what you can do is you can come up with a better idea if you've got a more aggressive or more undulant form of MDS and so in this case you can see where we look at the chromosome testing, if you have a deletion in chromosome 11 or deletion... complete deletion of chromosome Y in the MDS cells that the patients that have those abnormalities in the MDS cells tend to live for a long time with their disease on the order of 5 years. Now under the... So it used to be that if you had the "normal" chromosome gene result or the chromosome... result that it was an intermediate group. Well, under some new information that we have it tends to be leaning towards a better result that if you have a "normal" chromosome testing. So on the average, people can live about 4 years without treatment. This is without doing any treatment, just following along. Now, let's just jump down to the bottom and so if the MDS cells have complex. That means more than 3 chromosome problems in the MDS cells that is usually a very aggressive MDS and it's that form of MDS that usually progresses into a leukemia quite rapidly. So, in these people we might recommend going forward with a more aggressive treatment rather than just kind of watching and waiting.

So when you put all of this together, the chromosome results which is the cytogenetics, the blast percentage, the hemoglobin level, the platelet level and the absolute neutrophil count what you

can do is you can come up with a score, a prognostic score, for the patient and so generally on the left hand side you can see here that if you have very good... if you have mutations that portend for a very good prognosis, low amount of blasts, not that bad of a hemoglobin, not that bad of low platelets and your neutrophil count is above 800 or .8 then you're going to have a low score and low score means a longer duration of survival. It's the longest survival time with no treatment. The other side of this table if you have those complex chromosome abnormalities, if you have anemias, very low platelets, very low neutrophil counts, you're going to have a higher score and your survival time would be a lot shorter, again, if you do nothing but just follow along. So, if your score is low, good prognosis, average survival time 8 years... 8 to 9 years. That means half the people live longer and half the people might live shorter, but the average is 9 years and on the other side of the table if you have those complex chromosome problems, low hemoglobin, low platelets, average survival time is about half a year. So about 6 months or so. So and again, this is with no treatment. So, you can see how this is a very powerful tool because when we... this clarifies for the patient and for the doctor when we need to jump on some treatment and when we can just back off and just have you come back in a few months, we'll recheck the blood counts and then we'll go from there. So, that's how your doctor's coming up with that... this treatment plan.

The average age of diagnosis is 73. I told you about some recent research we're doing where we're finding that we're missing a lot of younger cases. So, we might find that MDS may be in the lower... upper 60s, lower 70s might be the new average. MDS is considered a cancer and that the only cure for MDS is a transplant. Even with a bone marrow transplant which is highly risky, but even with a bone marrow transplant the cure rate is only about 40 percent. So, it's not 100 percent even with a transplant and I'd be happy to answer questions about transplants. We do about 170 transplants upstairs in this hospital and Leslie Pettiford also has a lot of experience with transplant for MDS leukemia and we'd be happy to answer more questions later.

The most common cause of dying with people with MDS is actually low blood counts. It's not leukemia and so it's some complication of either bleeding or infection or heart attack or stroke and so that's why we do everything we can to try to boost your blood counts to prevent those and to prolong any of those kind of complications... to prolong the time of those complications.

So you might have... so when your doctor sits down with you, there's lots of considerations that risk stratification that I just went through, but also every patient is different and so if you atrial fibrillation and a low red cell count, the trigger at which we would give you a red blood cell transfusion might be a higher trigger. We're not going to let your blood count drop all the way down, your hematocrit, down into the low 20 percent. We might give you a blood cell transfusion if you're at the 25 percent or 28 percent hematocrit because of the heart condition, but I have younger MDS patients who I let their hematocrit drop down into the low 20s even upper teens because they don't have any symptoms. They still have a young heart. The other things that we look at in patients is whether you have other diseases, diabetes, if you have kidney problems. These aren't obstacles for us. They're just things we have to consider when we prescribe different medicines and to watch out for. As you know, your blood doctors and your cancer doctors first have to do training in general internal medicine and so we know how to treat most medical problems on top the oncology problem or the hematology problem.

So what are some treatment options? Well, for every patient it's supportive care always. So, transfusions, antibiotics, growth factors. Those are always the tools that we have, but we also have some newer therapies like Revlimid or Lenalidomide. We would prescribe that especially if you have problems in chromosome 5 especially in that situation and we have a trial here for patients that have low grade MDS. Even if you don't have a problem with chromosome 5, we will recruit you to a trial that we have where we're giving this Revlimid drug plus Prednisone. So we have a trial open for low grade MDS and if you are looking for a trial, I'd be happy to talk to you about that... Leslie will be happy to talk to you about that. Another drug is a low dose chemotherapy called Vidaza. We usually reserve this drug, this low dose chemotherapy, for people that have a little more advanced MDS or people that are requiring transfusions. We would then pull out the low dose chemotherapy and this chemotherapy works quite well. It's well tolerated. It's low dose. It's outpatient clinic. Some of you might be receiving it. Our response rate is about 40 to 50 percent, so that's pretty good. Half our patients get a response and we just completed a trial here where we have an oral pill form of Vidaza and, again, it was pretty well tolerated and the response rate was about 40 percent. So, we're encouraged. I think and my hope is that in this upcoming year in 2013, the FDA is going to review the data off of this oral Vidaza trial and we hope to have approval of this oral drug soon. Another drug is Dacogen. It's a cousin to Vidaza. The response rates are about the same and the Dacogen is given Monday through Friday whereas the Vidaza is given Monday through Sunday typically. We could also give other chemotherapy, some older chemotherapies from back in the 1960s and these can work as well. And next on the list is bone marrow transplant. So again, that's the only cure. All these other therapies that I mentioned can bring about a transient response, but eventually the disease will come back and for that reason we offer bone marrow transplant. Now, there's no absolute age cutoff for bone marrow transplant. The oldest individuals that I've transplanted were in their... were 74 both of them. What we do for people that are in their 60s and 70s is we give lower doses of chemotherapy as a mini transplant. So, their blood counts don't go down as low. They don't get all the toxicities from the high dose chemotherapy. The major challenge with mini transplant is that the disease can come back even after the transplant and so we have to modulate or modify the immune regimen after transplant a little more aggressively than as opposed to giving a full transplant. And then, of course, investigational clinical trial agents which Leslie will talk to you about clinical trials.

So again, some key principles. Transplant is the only cure. We'd be happy to meet with you and console and see if you're even a candidate for bone marrow transplant. A lot of times your doctor back in the local community practice will try to determine that without having to send you here to Shands or to Moffitt or Mayo, but if you're interested in having an evaluation as a second opinion, we'd be happy to see you. We do that quite often. Age alone is not an exclusion for transplant. The other point to make about treatment for MDS is that especially with Vidaza or Dacogen and actually even Revlimid is that the first few weeks of the treatment you may actually take a couple steps backwards meaning your blood counts might go lower. You might start requiring more transfusions before you start getting better. So, a couple steps back and then hopefully several steps forward is what we tend to see with our patients. Interestingly especially in the case of Revlimid, the people who get low blood counts initially from Revlimid, they're the ones that end up getting the better response on the long run. So, that's an... So your doctors should not be afraid of low blood counts and that it could actually be a good prognostic sign.

Okay. So, here is a diagram showing your blood counts and your bone marrow before treatment. If your blood counts are going down what could happen is when treatment is initiated is that your blood counts may go down even farther and so you can see in this graph the absolute neutrophil count will go down quite a bit around about weeks number four, five and six and then eventually the absolute neutrophil count will come up if you're responding and will stabilize. So, the message here is hang in there and hanging in there means hanging in there for possibly two, three, four, five months before giving up on a drug like Revlimid.... I'm sorry, on a drug like Vidaza. Revlimid should work on average after two months. Vidaza and Dacogen could take up to about four months to work. So, hanging in there for all kinds of therapy depending on the therapy depends on how long you need to hang in there.

Now, the early on when you initiate treatment, there may be some toxicities like you get a pneumonia and have to come to the hospital or you need transfusions or there's bleeding and that can be very discouraging because you're saying to your doc, "Hey, you're supposed to be making me better and here I am in the hospital with a pneumonia. What's going on?" So just realize that if you get through that initial period and keep going that about 40 to 50 percent of patients will eventually get a good response and can get off of transfusions and their blood counts can get higher.

So, just I'm going to go through these different slides quickly. And so I'm going to stop there. I'm going to answer some questions about treatment and then we're going to break for lunch and then have Leslie come and talk to us about how we can all stay healthy and I'll also talk about clinical trials. So, let me stop there and see if there's any questions. Yes, Melissa.

Q16: I'm her daughter. She is just newly diagnosed. What is our first step? How do I advocate to get her treatment when the doctor she has now says, "Well..." just handed her a paper and said, "You have MDS and I'll see you in six months."

Christopher Cogle, MD: Yeah. That's quite scary. So, Melissa is bringing up that her mom was diagnosed with MDS and the doctor handed a sheet of paper and said, "You have MDS. We'll see you in six months." That's very scary, very discouraging and it can be very disempowering, too. I agree with that. So, not all MDS has to be treated right away. That's one thing and so the question is whether or not the doctor thinks that your MDS, Marilyn, needs to be treated now or we can wait on the treatment. Six is a... For MDS, I agree, six months is a long time and especially for newly diagnosed. I think here is a case where you need to be your own best advocate and say call up like some other people in the audience will be and say call up and say, "Hey, doc. I know you wanted me to come back in May or June, but I'd like to see you earlier than that," and it's completely justified to do that. So, you need to call and make an appointment. I have my own doctors and if my doctor can't fit me in, I start shopping for other doctors because you're your best advocate. So, keep that in mind. Now, when do you initiate treatment? It's usually when the blood counts are going down, down, down and you're headed towards needing a transfusion. That's the most common reason. Other reason is that if you keep getting recurrent infections then that may be because of a broken immune system because of the MDS and treatment will help repair that immune system. So, that's another situation and a case where your low platelets, if you're having bleeding complications and bleeding can lead to a low red cell count. So if your platelets aren't working, you have broken blood vessels that are leaking and

that can leak out red blood cells. So, they can kind of tumble down together. So if your doctor... I don't know what the doctor's thought was, but the doctor might have thought, "Well, the platelets aren't that low and the other counts aren't that low. So, I'm not going to be that anxious about this and neither should you, so come back in six months." That might have been what they're thinking. You might want to call and say, "Hey, let me just come in for a lab check just so that I'm not as anxious about what's going on," and that's completely fine. Yes. Joseph, yes?

Q17: As far as you said if someone is treated with the blood transfusion in order to overcome this MDS and then later down the road, six months, whatever, they get it again. Okay. Is that like a trigger effect? Can they find out what the triggers are like chemo or something being a trigger to cause this MDS to come back?

Christopher Cogle, MD: So can you give me maybe some more specifics. So, is this your particular case?

Q17: Well, this is something I'm curious about. In other words if we do this, if we get a blood transfusion, 50/50 chance of overcoming this thing and then if she gets it again... If she gets it again because of her doctor giving her treatments that cause MDS.

Christopher Cogle, MD: Oh, okay. Are you referring to getting chemotherapy for a different type of cancer in the past?

Q17: (inaudible 1:28:18).

Christopher Cogle, MD: Okay. So, that's sort of a different situation. So in that situation, we don't know exactly why people get a secondary MDS. So, it may be because the bone marrow like a blood stem cell or a bone cell is not very good at recovering from the original chemotherapy radiation and so that could be the cause of why the MDS pops up at a later time. When the MDS pops up at a later time, again, there's only about a 5 to 10 percent chance of that happening but when it does happen we would not give the original chemotherapy again. We would give a different chemotherapy to try to get rid of that MDS. I don't feel like I answered your question. So, push me along.

Q17: Well, you did more or less and the question is is that. In other words if you go through the treatment, you go through the surgery and then later on how are these people getting it again? Recurring of cases. You said it's now only five percent.

Christopher Cogle, MD: Do you mean if a patient has MDS and they were treated and then the MDS progresses or relapses?

Q17: Yeah.

?: I think he's talking about transplants.

Christopher Cogle, MD: Oh, like a transplant for MDS. Oh, okay. So, now that... The answer to that is that the mini transplant, the low doses of chemotherapy that we would give for usually a

person 60 or above for MDS may not be enough chemotherapy to get rid of every last MDS cell on the inside of the bone marrow. Now, that may not be a bad thing because we are now going to rely upon the new stem cells that are transplanted in to make a new immune system to recognize the MDS cells and keep them away. That's where is a... That's an assumption and that's where the gamble is on a transplant that the new stem cells and the new immune system will be able to recognize those MDS cells as foreign and kill it. That doesn't always happen.

Q17: But you said that also a sign (inaudible 1:30:43).

Christopher Cogle, MD: In 40 percent of the time which actually is not most of the time. So, 40 percent. Yes?

Q18: I have a question. When the doctor tells you he wants to watch and when then you go ahead and take the chemo and then you tell him because you took the chemo, be ready to get another second piece. If you didn't take the chemo, the chances of you (inaudible 1:31:12) take the chemo you could get some other kind of cancer because you took the chemo.

Christopher Cogle, MD: Right. So, I'm not sure if that's a question or a statement, but it is true what you said. So, what she's bringing up is the very unfortunate dilemma that when you're diagnosed with a cancer like a lymphoma or a breast cancer that you are faced with if you take chemotherapy there's a risk of developing a second cancer. Yes, that is a risk that you have to take. Usually, the cancer that's in your face is scary enough that you want to get treatment right away. You need to, but everyone has to watch out and go for those blood count checks after you get treated for your original cancer, get those blood count checks and follow up just to watch your blood system in your bone marrow. Yes, ma'am.

Q19: (inaudible 1:32:13) talk about why you say bone marrow biopsy would show blasts, but the blood continued to be good. Would there be a reason that (inaudible 1:32:24).

Christopher Cogle, MD: Yes. So, the question was why a drug like Vidaza work in bringing up your blood counts, but there's still blasts in your bone marrow? So, the reason is because some blasts even though they are funny looking and they aren't the best at making red cells, white cells and platelets, they can make it if they're given the right medicine. The other thing is that some of the... so like Vidaza and Revlimid and Dacogen they don't just work on the blasts. They also have an effect on the normal blood stem cells and the normal progenitor cells and what they do especially Vidaza and Dacogen is that they open up the DNA to allow for more differentiation, more red cells, more white cells and more platelets. So, they open up the blood cells to make the early stem cells. They open them up to make more productive hematopoiesis. So, they basically turn on the factory is how to look at it. Even though there might be some residual blasts or a clone of blasts that are hanging out there that can still happen. Yes, sir.

Q20: Yeah. Along the same lines that my wife has it. I was diagnosed a year ago. I started treatment with Vidaza in March, went through exactly what you said in terms of 4 months my counts were down, down, down, my ANC was down to .3 and then last July all of a sudden everything started working real well and I had been having blood transfusions every 2 weeks until the end of July and I haven't had one since, but we had a bone marrow biopsy about a

month ago just to double check how that was doing and I went from 1 percent blasts up to about 12 to 13 percent which is good, but the blood work is great and within range and everything. It doesn't make sense and we can't get any answers (inaudible 1:34:46).

Christopher Cogle, MD: So, David is asking how can I have an increase in blasts in my blood count. So, the faulty thinking is that blasts equals dud cells and also the other faulty thinking is that there's nothing else in your bone marrow except for blasts. It turns out, so number one those blast cells are not just duds. Some blast cells can actually make hematopoiesis. They can make red cells, white cells and platelets, not very effectively, but they can do it. They can do some share of their work and drugs like Vidaza can help with that. The other thing is that your bone marrow is... those blasts are surrounded by normal blood stem cells which may actually have more room and be under the influence of that Vidaza to actually work harder and better than they have before.

Q20: Is this an indication that maybe after a year the Vidaza or after nine months, the Vidaza isn't really doing the job?

Christopher Cogle, MD: The question is am I losing ground with Vidaza? And the short answer is yes and you need to start looking to the next treatment.

Q20: Maybe Dacogen?

Christopher Cogle, MD: Well, let me qualify my answer. Yes, first. So, the issue is that the Vidaza seems to be working on the other cells in the bone marrow, but what may be happening is that there is a clone of MDS cells that have become resistant to the Vidaza and they have a survival advantage and so you're probably seeing them now as a dominate clone whereas before they were probably a very minor clone. So, that's the biologic explanation. Now, your treatment question is well what do I do next then? And that would require a discussion with you privately to talk about what your long term goals are, how you are with risk and so for example transplant is a risky procedure, but it's the only cure and there are some people that are of that mindset. I'm willing to take the risk if it means that's my only chance of cure.

Q20: I'm (inaudible 1:37:13) my mind to do that. I'm on a list.

Christopher Cogle, MD: For a transplant.

Q20: Yes.

Christopher Cogle, MD: Okay. So for transplant, on average it takes about two months to get you into transplant. So, the list is... within two weeks, we could have your HLA typing and then within a matter of hours we will be able to identify donors if you have one.

?: We have seven out of eight.

Q20: I've got seven out of eight, three donors, but the doctor was waiting for a perfect match.

Christopher Cogle, MD: So, you have three donors that are matching seven out of eight.

Q20: Yes.

Christopher Cogle, MD: And they're waiting for eight out of eight match.

Q20: Yes.

Christopher Cogle, MD: Okay. You may not have that time. With that big of an increase in your blasts with Vidaza in my experience you may not have a lot of time to wait and it depends where the mismatch is which... So now, we're getting into the real nitty gritty of transplant, but there's roughly... There's six different genes that I look at when I try to match a donor to a patient and there are some of those genes, about three or four of them that are really critical that we match them and there's the two other ones that it would be nice if it was matched, but it's not... We don't have to have them match there. So it depends on the gene level on the matching where you are with that. Who is your doc by the way?

Q20: Our transplant doctor is Dr. Deal up in (inaudible 1:38:56).

Christopher Cogle, MD: Up in Detroit. Okay. So, we have a doctor, Dr. Max Norkin (sp?1:39:02), who was at Carmodis (sp? 1:39:04) who now joined us... I want to say about three or four years ago and I'm not sure how long you're here in Florida, but you're... I can set you up with him.

Q20: Snowbirds.

Christopher Cogle, MD: Snowbirds. You're welcome to come and see Dr. Norkin. He knows the Detroit group very well. He might be a very natural fit for you if you'd like to see somebody. Thank you for your question. Yes, ma'am.

Q21: When we were in Miami, there was in the news things about a young family with kids that all of them were diagnosed with MDS and they were little kids. Has there been any research since them on hereditary?

Christopher Cogle, MD: Yes. So, the question is what about hereditary? There is. It actually when... I have a few patients that I believe have a genetic form of MDS. Now, most hereditary MDS most people with a very early form of MDS unfortunately don't live long enough to actually have kids and to spread it. So, it's very rare to have a family of MDS even though I know that there was... there's been a few that have been reported. I see a lot of spontaneous genetic mutations that happen in young... it crops up in... Well, the genetic event happens in the embryo, but that the low blood counts don't come about... don't get identified until the individual is in their young teens and they have fatigue or a lot of bruising and then they come in with low platelets at the age of 16 and then we work them up and find they have MDS and then I... So, I collaborate with a laboratory in Baylor University and we do genetic testing to find out if they... what kind of germ line gene mutations they have. So for example, when we do the bone marrow biopsy, we send that off with for the chromosome testing, but only looking at the cancer

cells. In my young patients with MDS, I do a buccal swab at looking at more than just their cancer cells, but what they've actually inherited and then if I identify, for example, there's a gene called RUNX1. If that gene is mutated, I then check their mom and dad and see if they have the RUNX1 mutation and oftentimes they don't and that it was a spontaneous mutation and that poor child during when they were embryo that just made them susceptible to developing MDS at a young age. Now, how that's changing our practice is that we now have a collaboration with a fertility expert here at Shands. Her name is Dr. Alice Wooten. She has an onco-fertility program where we do sperm banking. We also do ovarian... ovary storage for these individuals because what we can do is... if we can get them to a transplant to get the... and cure them of their MDS, later on when they want to have kids what we can do is we can select out sperm or fertilized eggs that don't have their mutation in order for them to have their own kids without MDS. So, that's called preimplantation genetic diagnosis and it's obviously very cutting edge.

Leslie Pettiford, RN: Just introduce myself. My name is Leslie Pettiford and I work here with Dr. Cogle in the Research Department with bone marrow transplant and the blood cancer patients. I've been a nurse for about 15 years like he said. The majority of my nursing experience has been with bone marrow transplant and leukemia patients and I've been in the research side of it for about 6 years now and I mostly do MDS and leukemia specifically with Dr. Cogle. So, they asked me to spend some time specifically on this one slide. So, we're going to talk about how to stay healthy with MDS.

So one of the biggest and most important things is eating a balanced diet and it can be hard if you're working or if you don't feel good and you just...you don't want to cook. It's easier to get takeout, but eating the proper foods actually nourishes your body and gives you energy to get through the day and helps really combat a lot of the symptoms that you experience. When you have MDS whether you're on treatment or not and it really helps combat fatigue and illness. The key pieces to a balanced diet are incorporating hydration, drinking enough fluids every single day; eating fruits and vegetables; whole grains; low fat dairy products and really limiting your amount of sugar and processed foods. So, these are all things we all should do every day, everybody in this room whether you have MDS or not, but it's really important when you have a blood cancer to really try to maximize everything that you put in your body. Everybody in this room is going to have a different experience with their MDS and your nutritional needs may be very different from the next person. Some people may experience a lot of nausea with their treatments. Some people may have no... any nausea. Some people may just not want to eat. Some people may have vitamin deficiencies. So, really talking to your doctor, being active in your care and knowing what's going on with your body is really important and another really good thing to do is if you are having nutrition issues is to get in touch with a dietician or a nutrition specialist to help them formulate a plan for your diet. Patients who have very low white counts, when you ANC, the neutrophils, those are your mature blood cells in your body that help fight infection. When those counts are very low, you have to follow a special diet and you'll have to... it varies by cancer center and by physician, but so speak to your physician to what he wants your lower limit of your ANC to be for you to follow a special diet, but the special diet involves basically no fresh fruits or vegetables, no raw meats, no nuts, nothing out of a... carbonated fountain drinks, no ice creams out of a machine. So if you want to have ice cream, buy it hard packed from the grocery store. If you want a soda, buy it with a lid or a tab top. Don't go to McDonalds and get it out of a machine because we or you don't have control of how often they clean those machines and they harbor bacteria and when your white count is low, you're at higher risk for infection. I'm not telling you these things to scare you. These are recommendations when your doctor tells you that you need to follow a special diet.

Q22: What was the nuts?

Leslie Pettiford, RN: This varies by cancer center, but some nuts are not processed and you're at risk for... they could have mold or other things in the containers and when you don't have an immune system to fight infection you're at risk for getting sick from eating those and nuts actually expire. So, you can't keep nuts indefinitely in the kitchen. So when your counts are low, I would recommend not eating nuts.

Q23: Would you stay away from salad bars?

Leslie Pettiford, RN: Good point. Thank you for bringing that up. I would stay away from buffets when your counts are low. You don't know who's touched the tongs, who's touched the food, is the food kept at the right temperature. So, those are the key things, buffets, soda fountains, ice cream machines. We have patients here that have low counts every single day of the week and some people just want a milk shake. You can have one if you make one yourself at home with hard pack ice cream in your own blender. Just don't go to McDonalds and buy one. Nothing against McDonalds. Sorry. I guess I should put that as a disclaimer. So, those are just tips and ask your doctor if you need to be on a neutropenic diet. They'll advise you on what is right for you.

Another thing is a lot of people with MDS worry is it okay to eat red meat. It is, but we want you to vary your protein choices. So, make sure you have fish, cooked fish, if your counts are low; beans; peas; other sources of protein; low fat dairy products that have been pasteurized. Don't just eat red meat and if you do want to eat red meat, make sure it's cooked well done when your counts are low.

If you are taking cyclosporine as part of your MDS treatment, you need to avoid grapefruit juice or grapefruit. Grapefruit could increase your levels of cyclosporine in your blood and make it... it's more difficult to process the amount of cyclosporine in your blood when you consume grapefruit.

Supplements. Anybody in here take vitamins? Anybody in here take herbal medications? St. John's Wart, Echinacea, garlic. Do your doctors that you take them? Very good. Always make sure your doctor has a list of everything that you're taking. Some of those medications can interact with your treatments. Everybody needs to be on the same page. Some people think because they're vitamins or supplements that they don't need to tell their healthcare providers that they're taking them. They're very, very important. One specific is if you have low platelets from your MDS. Avoid taking high doses of fish oil. Fish oil can make your platelets slippery. What happens when you have low platelets? Your blood doesn't clot as well. So, on top of the fact that your blood's not clotting well, if you make your platelets more slippery, you're going to have a harder time clotting if you cut yourself or something happens. Also, avoid taking iron supplements. If any of you have gotten a blood transfusion as part of your supportive care, you've gotten enough iron for about two years. You don't need to take any extra iron.

Q24: My doctor I'm low on iron and I have three blood transfusions, he gives me iron pills and I (inaudible 1:50:55).

Leslie Pettiford, RN: Iron is something specific that your doctor may or may not want you to take, but iron can also... it has other side effects. It can make you constipated. It can interact with chemotherapy and if your platelets are low and your constipated there are then further issues that can occur and you need to... that's why I want to really reinforce talk to your physician about any medications before you start taking them and like I said, keep a list of your chemotherapy medicines that you take. Keep a list of your non-chemotherapy medicines that you take. If you take Tylenol, if you take Zantac, if you take... if you're on an antidepressant medication, if you're on heart medication. Make sure that you always have a current list with you

whenever you go to the doctor so that everybody's on the same page and share it. Make sure if you have a caregiver that goes with you to your appointments that your caregiver knows what your medications are that you take.

Q25: I just had something to me just recently where another physician prescribed a necessary medication that he did not know was going to be a problem with medications that I'm on through my oncologist. If I had not checked with my oncologist, potentially something bad could have happened there and I wouldn't have necessarily thought that. I would assume the other doctor even though he had a specialty in another area would know, but he didn't know.

Leslie Pettiford, RN: You're absolutely correct, Nancy. Thank you for bringing that up. A lot of physicians who are not oncologists or hematologists have no idea about the medications that we use to treat MDS or leukemia and that's because they're not specialized. They don't know or they have very basic knowledge and so they may not know all the very specific interactions that a very benign medication that they may prescribe for something else that you have going on may actually interact with your cancer treatment and one really good resource is your pharmacist when you go pick up your medications. Always discuss with your pharmacist what are the interactions. That's part of the job of a pharmacist. It's not just to hand you your medicines when you go to pay. Part of their job is to inform you of the medications that you're taking, do you have any questions and these are potential interactions and these are the symptoms that you may want to look for. If you still have questions before you take the medication, you should always call your oncologist to verify is this medication okay for me and then your oncologist or hematologist can always call that physician and say, "Does she need..." Do you, the patient, "need to be on this medication or is there an alternative that may not interact with the treatment that the patient needs to be on for the MDS," and then they can have the discussion of what should... what medication you should be on. Thank you. Good point.

So moving on. Activity, exercise. How many people in the room exercise? I'm not going to raise my hand. I'm not going to lie. If walking back and forth at the hospital counts as exercise then I'll take it, but I don't think it does. Exercise. Three to 5 times a week of about 30 minutes if you can tolerate it is the recommended amount of exercise that anyone should do and it should be to your physical level. I'm not saying go out and run a mile or 4 miles or 10 miles, but just walk around the block if you can. For some patients that's just getting up out of the chair at home and walking to the mailbox and walking back. If you can do that once today, maybe twice in a few days, 3 times next week, you're going to help your body build up some stamina and that's really important when you're going through treatment. Exercise has been proven to decrease emotional distress and fatigue although it seems kind of counterintuitive that exercise would actually increase your energy, but it does. It gets your body conditioned to doing more and when you exercise and you take deep breaths in, you're increasing the amount of oxygen that those red cells are getting and with MDS not all your red cells are functioning great. So, increased oxygen, you're going to feel better, you're going to have a better day. Always discuss with your healthcare provider before you start any new exercise program. Make sure you have permission. There are certain times when you shouldn't exercise depending on your blood counts. If your platelets are too low, I don't want you going out and riding a bike, but a walk around the block should be okay. If you have a central line or a pic line for your treatments I don't want you going swimming in the pool. You could get an infection. So, make sure you discuss with your provider

what's the right exercise plan for you. The primary goal with exercise is just to get moving. Get out of the chair. Stop watching TV. Just get some fresh air.

Sleep. Sleep is really important when you're going through treatment. One-third to one-half of all cancer patients experience a change in your sleep patterns. Getting enough sleep improves your quality of life. It decreases fatigue, it increases energy, makes you feel more positive. I know when I don't get enough sleep, I am cranky and I can't imagine on top of that piling on the fact that I have MDS and I'm getting cancer therapy and all these medical bills and all these other things are going on. So, really making yourself a sleep plan can help. Try to aim for 7 to 9 hours of sleep every day. Try to aim for the same bedtime and the same waking time. It's really important to get your body on a schedule. Also if you need to take a nap, they recommend only taking a nap for 30 minutes. I can't take a nap for 30 minutes. If I take a nap, it's at least got to be an hour, but they say the longer you sleep during the day, the more difficult it is to go to sleep in the evening. Also getting in that exercise will help you sleep better at night. Another way if you are having difficulty falling asleep. Some people say having about 30 minutes to an hour every evening before bedtime of just relaxing. Disengage from anything around you. Don't watch TV. Don't watch the news. Don't read some intense book. Just go relax. Maybe listen to some nice music or just have quiet time. Try to de-stress. If you still try all these things and try a sleep plan and you're still having difficulty sleeping, there are other alternatives that your healthcare provider can discuss with you such as medications or alternative therapies. Some patients do yoga or acupuncture or hypnotherapy. There are other things out there and just make sure you discuss those things with your provider before you engage in them.

Avoiding infection. That sounds really scary. When your counts are low, you're at risk for infection because all your little white cells that fight infection, they're not there to help you and so you have to take control and manage that. You have to limit your exposure to infections. One way to do that is staying away from crowds, limiting where you go. It's not ideal, but when your counts are low, you don't want to risk getting an infection. However if you have to balance that with the quality of your life. If it's really important for you to get to church on a certain Sunday and you know the church or synagogue or wherever you're going is going to be really crowded and your counts are very, very low, wear a mask, wash your hands, go right as the service is about to start, leave right as the service is ending. Avoid everyone and shaking their hands and giving them hugs and kissing them on the cheek to say hello, how are you, but if you really need to have the desire of going for the service or the wedding or whatever it is, you need to do that. You're supposed to have a good quality of life even though you're going through cancer treatment.

Basically, I guess what I'm getting is use your common sense. Avoid people that are obviously sick. So, say your neighbor brings you dinner or you guys talk once a week. She calls, sounds horrible, coughing, coughing, coughing, but you feel bad to tell her, "Uh, probably not the best time to come over." Guess what? You are your advocate. You have to tell them, "I'm sorry. If you're sick it's probably best that you don't come over this week. I really appreciate you taking the time and energy to come be with me or do these things for me, but it's actually better for me if we avoid each other this week. I don't want to take the risk of getting sick."

Carry hand sanitizer. I see some of you have the little hand sanitizers on your bags. Take them everywhere. They don't replace washing your hands. Wash your hands as frequently as you can with actual soap, water and a paper towel, but in the event you don't have soap, water and a paper towel, hand sanitizer is a good substitute. If you ever... most people have cell phones in this day and age, but if you ever have to touch a public pay phone, I recommend don't. Use your hand sanitizer even after you wash your hands in a public rest room, use your hand sanitizer after you leave. When you go to the grocery store, use your hand sanitizer. Also use the wipes if they have them. The other thing is being around children. Many people in this age group have grandchildren if not great-grandchildren and it's very important to stay connected with your family. Most of the time it's okay to be around those children. However, children are germ factories. They carry all kinds of things. Just be careful. If they obviously have a runny nose and a cough I wouldn't play with them that day. I would really avoid them. Also if they've had a vaccination recently and it is a live vaccine, you should not be around them when your counts are low. You should discuss specific recommendations about being around children with your healthcare provider, but most people with MDS and leukemia can enjoy their family and you should because it's important and you have to, again, balance your quality of life with what you're trying to do to stay healthy.

Avoiding bleeding. So, how many people in here have low platelet counts as part of their MDS? So, not that many of you. Very lucky. So, low platelet counts are also known as thrombocytopenia. Again, one of those big words, but Dr. Cogle likes those big Greek words. So basically, it just means low platelets. So, platelets help keep the body from bleeding when you cut yourself or you injure yourself. So, the platelets stop the bleeding by clumping together and forming little plugs in veins, arteries, anywhere that you've cut yourself. So when your platelets are low, you're at risk for bruising, bleeding, anything of that sort. So... yes?

Q26: And the others, the family practice had me a low dose aspirin (inaudible 2:04:25).

Leslie Pettiford, RN: Thank you. That was actually the next point I was going to make.

Q26: (inaudible 2:04:30).

Leslie Pettiford, RN: No, no. Thank you. No. Absolutely.

Q26: (inaudible 2:04:32).

Leslie Pettiford, RN: Yes. Very good point. When your platelets are low, your oncologist or hematologist is going to, again, want to know all of the medications you're taking. If your general practitioner doctor or your cardiologist had you on an aspirin regimen based on your cardiac history or that you've had a heart attack in the past or a blood clot or anything else, your hematologist may actually at some point have you stop taking medications such as aspirin or ibuprofen or any medicine that can cause a problem with the platelets. Another medication is Excedrin. Some people don't know that.

Q27: (inaudible 2:05:23).

Leslie Pettiford, RN: Yes. Pepto-Bismol has aspirin in it. So, there's a lot of medications out there that can cause problems with platelets. Again, I can't reinforce it enough. Before you take any medication, contact your healthcare provider and make sure it's okay that you take it.

Q28: Alka-Seltzer too has aspirin, doesn't it?

Leslie Pettiford, RN: Yup. So, if you're having issues with reflux or indigestion or sometimes you can just go to the pharmacy department and get an over the counter medicine. Talk to the pharmacist. They're not just for prescription medication. They're there to help you understand even over the counter medications and if it's your regular pharmacist, have a conversation with them. Remind them what medications you're taking. Remind them that your platelet counts are low. What over the counter indigestion medication is appropriate and then you have their feedback and then you can also verify Dr. Cogle or Dr. Bodia (sp? 2:06:28) or whoever your oncologist is is it okay for me to take some Zantac because after I eat a really big meal on Thanksgiving, I have some reflux or indigestion and it's just... I feel uncomfortable.

Q29: What (inaudible 2:06:42)?

Leslie Pettiford, RN: Benadryl is fine to take. Many patients actually have to take benadryl when they're getting blood transfusions to prevent reactions. Benadryl is okay drug. It's an antihistamine and there's nothing in benadryl that would interact with your MDS or the therapies.

Q30: I get very anxious. I get twitchy and everything when they give it to me.

Leslie Pettiford, RN: If you do, I would let them know there's alternatives to benadryl that they can give you. Does everyone here know what the signs and symptoms are of low platelet counts are? So if you started having some symptoms, you'd know what to do or...? So bruising. Everybody bruises every now and then. You stub your toe on the chair in the middle of the night when you're going to the bathroom, but excessive bruising just doing daily things like unloading the dishwasher and you rub up against the counter and you get a huge bruise on your arm or anything that seems like excessive and they're not going away and they're just getting worse. Bloody nose. Huge sign of low platelet counts. You need to call your physician when you have a bloody nose. You need to get your counts checked. Pinpoint red dots on the skin are another symptom of low platelet counts that kind of just look like little red dots usually on the legs, sometimes on the arms, sometimes on the chest but it's usually the legs. Blood in your urine or your stool. You guys should pay attention to those things. Frank blood sometimes is not an indicator that your platelets are low. You might have a hemorrhoid, but pay attention. Bleeding gums. Do you guys use soft toothbrushes when you brush your teeth not a hard toothbrush? It's really important. Your gums are really sensitive. You want to take care of them. Cuts that won't stop bleeding. So if you're chopping carrots, you're making dinner, you cut your thumb and usually a couple of minutes you're good. You got your band aid on, you're back to cooking dinner. Well, that cut's not stopping. It's bleeding, bleeding, bleeding. Your platelets are probably low and you need to get checked or if you're coughing up blood. You need to go ahead and contact your provider and possibly call 911.

Your healthcare providers may recommend platelet transfusions to reduce the risk of bleeding and it depends on how low your platelets are and it depends on your medical history. If you have a history of stroke or if you have a prior history of bleeding or there's all kind of situations where the physicians you may have a higher number for the threshold in which they transfuse you. So, that's something you'll discuss with your physician. Typically here with Dr. Cogle, we don't transfuse people unless their platelets are lower than 20,000, sometimes down lower than 10,000. Depending on the history though, they may bump you up to 50,000 and you need a platelet transfusion. It just depends on the scenario and what's going on.

Platelets are considered a form of supportive care and they do not change the characteristics of your MDS. They're also only temporary. One platelet transfusion doesn't last very long. For some patients, it might hold them for a few days, a week. Some patients it only holds them for a few hours. So, repeat transfusions may be necessary until the medications that you're receiving, the treatments that you're receiving for your MDS are getting the disease under control and your bone marrow is able to make the normal cells. The number and frequency of transfusions will vary just like everything else that you guys are starting to experience with the disease process and your healthcare provider like she said with the aspirin won't recommend that you stop taking antiplatelet medications when your platelet counts drop very low.

Does anybody have any questions about platelets? Okay.

Continue to enjoy the things you love. Like I said, go to church, go to weddings, see your kids, see your grandkids. If you like to garden, if your counts aren't low, go ahead, do it. Be active. Enjoy your life. You don't have to just sit in your house on the couch because you've been given a diagnosis of MDS. Take advantage of the available resources to you. Seek out supportive groups in your area. The MDS Foundation has a great website. There's a lot of stuff out there. You just have to be active and find it.

Also, ask for help when you need it. I know a lot of people in this room probably don't like to ask for help. You have to. There comes a time where you just need help even if it's just for somebody to get your mail for you or come over and vacuum your house because you just don't feel good and ask for the help. More people than you know would probably be willing to come and help you. Sometimes you have to just to let them know that you're willing to accept the help.

Also be active in the participation of your care. Do research. Ask questions. Don't just sit back and say, "Okay," when they give you a prescription or say, "This is what you need to do." Seek out treatments. Seek out care groups. Seek out anything, but be an active participant in your care and don't let anyone just dictate what you have to do.

I think at this time Dee and Sandy want... They'd like me to show you guys the online version of the *Building Blocks of Hope*. So for any of you guys that like to play around on the computer or have an iPad or a Kindle. I know a lot of people are starting to use a lot more electronics. The book that you guys received today is also available online. So, this... it's not finalized on the Internet yet, but you can go to the MDS Foundation website. Oh, it is final... This is the website. It says demo still. Not licensed for public use. We have a celebrity on the room. I'd like just to let everyone know. He's actually in the book and on the videos online about his own experience

with MDS. This is Otto and he's had MDS for 15 years. So, he's a good resource for those of you that are newly diagnosed and still trying to learn how to cope with what's going on. He's had a lot of experience. He's gone from what he was telling me was when there was no information out there 15 years ago about MDS, no clinical trials, nothing and to now be available to resources that are out there and really this *Building Blocks of Hope* is to really help you guys especially the patients that are newly diagnosed know that this is not the end of everything. You still have your life to live and engage and live your life. So, I want to show you guys the book and if you have a tablet or an iPad, it is where you can just flip the page just like on a Kindle or an iPad, but if you don't and you want to use it on a regular computer, you just click it. You can make the page larger or smaller and then you can just turn the page and you can click it and make it smaller. So, I'm not going to go through all 140 pages of the book. I'm not, but I did bookmark... It's bookmarked on my computer at home. But anyway, they really wanted me to just kind of show you how interactive it can be and the online version is just like what you guys got in folders today.

This is the MDS Foundation website. It's got a lot of good resources on it and it's got a whole section for patients and visitors. It talks about upcoming events, patient and family forums, the *100 Questions About MDS* booklet. It talks about insurance. I know that some people end up having insurance issues going through medical treatments. This is a good resource for you. It also gives you the MDS Centers of Excellence, so you know if the facility that you're receiving your treatment has been designated by the MDS Foundation to be a Center of Excellence. Just a little side note. We are a Center of Excellence here at UF and Shands. So, that's the website.

And then do you guys have any questions about staying healthy or the *Building Blocks of Hope*?

Q31: What about sugar and salt?

Leslie Pettiford, RN: Well, like I said. Use your common sense. Everybody wants to limit sugar.

Q31: But it's in everything, cereals, everything.

Leslie Pettiford, RN: It is, but your body needs some sugar. I would if you have a lot of questions, I would suggest meeting with a dietician to see what the right amount of sugar is for you, but if you incorporate whole grains, lots of fresh fruits and vegetables if your counts allow it and then limited sugar. Use it as a reward system. That's what I have to do.

Q32: (inaudible 2:17:41) meal. Kind of refrain from eating a lot of prepackaged (inaudible 2:17:48).

Leslie Pettiford, RN: Yeah. Really, you want to get down to eating fresh food, food that you make at home and stay away from... and that's for everyone. It's not just for patients with MDS or leukemia. We all need to follow those diet guidelines. Any other questions? Otherwise, Dr. Cogle really wants me to kind of give you guys an introduction to clinical trials and participating on them. I'm not going to discuss any specific clinical trials, but just an overall overview of what a clinical trial is. It seems a lot of patients that are out in the community and that are not at larger academic institutions may not know what all involved with clinical trials.

So, there's some really good resources for you if you are interested in clinical trials or finding out what's out there and available for you. The first website that I've listed is clinicaltrials.gov. The second one is cancertrialshelp.org and cancer.gov and so these three websites are the main ones I've used today to put together the slideshow.

So, what is a clinical trial? Does anybody in here know what it is? Has anybody taken part in a clinical trial? Congratulations. So, a clinical trial is a study that usually involves human volunteers that are also called participants. It's intended to add to medical knowledge. So, there's two main types of clinical studies. There's clinical trials and observational studies. Most clinical trials study new therapies to evaluate the safety and effectiveness in humans for a certain disease. Trials have to follow a careful set of steps that allow for the gathering of the data to answer the questions that the scientist has formed based on lab experiments and preliminary trials. Some clinical trials explore looking at a new therapy and comparing it to what we already know works and it's to see is the new therapy better and if so then it can replace the standard therapy and it becomes the most new and innovative treatment. Clinical trials using drug development are described by phase. There's four phases and these phases are defined by the Food and Drug Administration.

So, phase one. Phase one is first time in human subjects. The trial is designed to determine the dose, the route of administration meaning is it given by mouth, is it given by IV, is it given by an injection? Schedule of administration meaning how often is the drug given. Is it given daily, weekly, monthly? In this phase, the researchers also begin to determine is the drug safe. So in noncancer clinical trials, phase one is usually done in healthy volunteers. Those volunteers are generally young males. In cancer clinical trials, phase one studies are done in patients with cancer. We can't give cancer treatments ethically to people who don't have cancer. So, it would be unethical and harmful to healthy volunteers to give them an experimental cancer therapy.

Phase two trials. You get an established dose and a basic safety assessment of a drug. So you go onto phase two and you get to explore more about the drug and how it interacts in the body and the side effects it causes and so you really get to determine the effectiveness of the drug. Is it worth pursuing? Are patients seeing responses? So if a drug passes phase one and phase two then generally it's seen as pretty safe and effective in patients that it's trying to treat.

So, then we'll go onto phase three. Phase three clinical trials, the treatment is either tested alone or against an approved standard therapy and typically phase three studies enroll very large numbers of patients, hundreds and hundreds and hundreds of patients and so for cancer studies these studies have to generally be if not just nationwide here in the United States, but worldwide because as you guys know MDS only affects a certain amount of the population and so to effectively see if a drug works we can't just rely on the few people who qualify in the United States. They generally have to go outside. We see a lot of patients in Europe, in Asia in clinical phase three clinical trials. Phase three clinical trials if it involves a comparison, it's usually randomized. Randomized means it's being assigned by chance similar to the flip of a coin. So, you would be randomized to the new therapy or the standard therapy. In cancer treatment, generally you are going to get the bare minimum what is standard of care therapy plus or minus the new investigational therapy.

Phase four. Phase four studies are not that common. They're usually done after the FDA has already approved a drug for therapy, but sometimes the FDA requires the drug manufacturer to do further research on the drug to see if it's having long term side effects on the patients. Sometimes phase four studies involve a cost analysis. We actually have a physician here that's doing a cost analysis on a new drug that we use to collect stem cells and he's seeing his hypothesis is getting the drug to help collect stem cells more cost efficient than having to do multiple collections for stem cells. So, phase four is done later after the drug has approval.

Who pays for clinical trials? Well, most of them aren't free. Most of the time the sponsor or the drug manufacturer doesn't pay 100 percent. Sometimes they pay almost everything, but depending on your type of insurance before you agree to participate in any kind of clinical trial, you need to confirm whether or not you will be responsible for any costs associated with the clinical trial.

Patient care costs. Those are costs that are related to treating your cancer whether or not you're in a clinical trial. These costs are most often covered by your normal insurance. These costs include doctor visits, hospitalizations, routine lab tests, x-rays, anything that you would be normally receiving if you were getting regular cancer therapy.

Research costs are those that are specifically related to taking part in a clinical trial. These costs are usually not paid for by your insurance, but they may be covered by the trial's sponsor. Research costs can include the actual drug you're receiving, lab tests that are performed purely for research and any additional diagnostic tests that are performed solely for the trial.

When you take part in a clinical trial, you may have extra doctor visits that you wouldn't have with standard treatment and these extra visits can add costs. Transportation, gas, lodging if you live far away from where you're participating on the clinical trial, time off work, childcare if you have kids. So, when you're thinking about going on a clinical trial, you'll need to really make sure to educate yourself of what are all the things involved in being on a clinical trial if there's extra visits and if there's compensation for those visits.

So in the State of Florida, there is a clinical trial compact that was passed July 1, 2010 and this compact says that certain insurance providers have to cover phase two, three and four clinical trials for cancer if the physician says that you need to participate. These providers in the State of Florida include Humana, Blue Cross/Blue Shield, AvMed, Vista, Aetna, Cigna and United Healthcare. They are not required to cover phase one clinical trials at this time unfortunately, but we're working on changing that.

Routine care costs. We already kind of gone over this. We're not going to go over this part again. Actually what this is just saying that the key provisions of the compact saying that the insurance companies that voluntarily put themselves in the compact have to pay for the routine care costs if you're on a clinical trial. However, they exclude the drug, the devices, nonclinical expenses and items or services purely for data collection which is all when they're doing the pure research. Many times the... in most scenarios if you're on a clinical trial, the sponsor provides the drug free of charge. However if it's an IV drug or an injectable drug, the act of you receiving the

medication in the clinic or the hospital usually is billed to your insurance company. Usually just the sponsor pays for the medication itself.

How do insurance companies decide whether or not to pay for clinical trials? Well, they have board meetings or whatever they do and they decide the risk of putting patients on clinical trials and then they write it into their policy. So if once you've decide you want to participate in a clinical trial, you need to read your policy, you need to find out, make contacts with your care manager at your insurance company. Some insurance companies say they can only participate in a clinical trial if it's medically necessary and this is often only decided case by case and through physician to physician phone calls. Sometimes they'll deny it. Appeal it. Don't let them say no the first time. Oftentimes we get involved as study coordinators to help patients get clinical trial coverage for medically necessary treatments. Some insurance companies say, "Hey. There's no more standard therapy for your type and stage of cancer. Okay. We'll pay for this newest treatment out there even though it's experimental," and some insurance companies say, "If it's sponsored by the National Cancer Institute, we'll cover it."

Insurance issues. There's a lot of insurance issues when you have cancer. You get all these bills. You get bills from the hospital. You get bills from the clinic. You get bills from your physician. You get bills from the lab. You don't know if they're right. So, work closely with your doctor if you are in a clinical trial to make sure that you're being billed for the right services.

Maintain open communication with your research coordinator or your research nurse. That person should know everything that is paid for by the study and what should be billed to your insurance company. If something is billed in error, your coordinator can help you get that corrected. They can contact the hospital, the lab, your insurance company and get the bill corrected.

Work with your insurance company. Some insurance companies just simply need preauthorization. They just need a phone call saying, "I want to do this." Make sure they get that if that's what they require otherwise you run the risk of voiding all of your insurance benefits. Some insurance companies need a letter from your doctor and a copy of the inform consent. The study coordinator can help provide those things and get them directly to your insurance company.

Deciding to take part in a clinical trial. So, some people want to know like participating on a clinical trial, does that just mean I don't have any other options? Absolutely not. There are some patients who've exhausted all their standard therapy options and clinical trial is ultimately what's left for them, but many patients it's not. There's a lot of therapies out there and clinical trials, it takes average to seven to nine years to get a drug from a phase one study where it's used first in human subjects to phase three where the FDA is finally going to approve that drug. Phase two and three studies can last for many years and they can already be showing effectiveness. So if your doctor or the institution that you're going to if they have this new therapy and it's... they know it's starting to work for patients with your disease type, explore it. Empower yourself. Get the knowledge.

Some benefits of taking part in clinical trial is you'll have access to new therapy. Also the research team watches you like a hawk. I can't tell you. I mean, I want to know everything about my research participants. Did you have gas? Did feel a headache coming on? Everything. Did you not sleep well today? You want to provide the best care and you want to get as much information, so we've known this side effect is really the drug or is it your disease process? If the treatment that's being studied is more effective than the standard therapy, if you enroll in a clinical trial you have the ability to be one of the first people to benefit from that new treatment and some people just participate in clinical trials for altruistic reasons. They just want to help people in the long run because 20 years ago, 30 years ago, there were people participating on clinical trials that enabled you guys to have the therapies that you're getting now.

Risks. Nothing you do in life is not without risk. New treatments might not be better than standard treatments. They might be worse. They might be more toxic. That's why we're doing clinical trials. You may be required to make more visits to the doctor or the clinic or be required to be hospitalized and you have to weigh those things against your quality of life and whether enrolling in a clinical trial is worth it for you when there's these extra costs. Also if your health insurance may not cover all of the patient care costs associated with a clinical trial then it may not be beneficial for you because most of us in this room don't have an unlimited bank account to just pay our healthcare bills.

Who can join clinical trials? Well, it's very specific. Not everyone who has MDS can enroll in any MDS study. So, you have to have a certain type of cancer or a certain stage of cancer. You have to have received or not received prior therapy. You might have to be in a certain age group. You might have to... If you've had a history of heart attack or stroke, you might not be eligible for a certain drug therapy because there may be risks that we don't want to give you those drugs and your current health status is also affected.

This is just a list of questions to ask your physician or healthcare provider about treatment and clinical trials. Don't ever let a physician just hand you a consent and say, "I think you should participate on it. Do you want to do it?" Read the consent form. Ask questions. Find out what the treatment is and find out what's its track record. Go on the Internet. All that stuff's on the Internet. Clinicaltrials.gov. It's a great resource.

I've gone over most of the stuff already. Another thing that we really reinforce with the clinical research is that it's voluntary and if you feel like you're being coerced into treatment then the trial is not for you. Also we try to keep all of your health information as private as possible, but we do share some information depending on the phase of clinical trial with places like the FDA and other cooperative groups or other physicians. Make sure you know and understand the costs of the treatment of the clinical trial. Make sure you were told any alternative therapies to the clinical trial.

The Affordable Care Act. So, effective January 1, 2014 as part of the Affordable Care Act or a lot of people refer to it as Obamacare, anyone wanting to participate in a clinical trial will be eligible and you will have complete insurance coverage. This applies to all clinical trials that treat cancer and other life threatening conditions. So, that includes phase one. It includes all your care costs. Your insurance company is going to have to cover them.