Speakers:
Suman Kambhampati, MD
Jean Ridgeway, DNP, APN, NP-C, AOCN

Jean Ridgeway: So, this is just to kind of give you a little bit of a glimpse of some of my other colleagues internationally that go… that do this as well. So, we've got folks in the UK, in Italy…

Q1: In Tucson, Arizona.

Jean Ridgeway: Yeah and so people all over the country that do this very thing and so *The Building Blocks of Hope*, the book itself actually was a venture authored by all of us. So, we all contributed to creating it. Anyway. Alright. So, looking at a number of these questions. So, that's what we'll talk about and Dr. K talked a lot about this and I would encourage you to pick up one of the books. They're also available online in a PDF document. So if you're an electronic person and you want it on a tablet, you could do that as well and I think part of owning the characteristics of your health is really getting a better understanding of what type of illness do you have and so really getting to understand not only the globalness of MDS, but where are you? This, (Attendee), tells us that she has 5Q-. So, she knows that and so some of the things that we've heard today we know that that as one of the subtypes in MDS can be treated with Lenalidomide and acts a little bit differently than some of the other MDS subtypes. So, you should… it would be probably help you for you if you know like what disease you have and when you were diagnosed if you can get the IPSS score and there's actually if you go to the MDS Foundation website, you can actually put all of your information in from your pathology report and come up with your score. Now, that score is done initially. That's when it's valid. So, you don't rescore yourself as you go on. You get scored at the very beginning of your diagnosis.

Q2: So, the scoring happens at the beginning. Your score doesn't change.

Jean Ridgeway: That's correct because that's the starting point of where you're being diagnosed and how you treatment plan is going to be coordinated.

Q2: Okay. All through the course of the disease, you're going to stay at that unless change something like have a bone marrow transplant which could…

Jean Ridgeway: So when you get the diagnosis, it pretty much… it kind of stamps you with a label. So for instance, if you have RAEB1. So, you have refractory anemia with excess blasts type 1. That's what you were diagnosed with and as treatment starts, say even with Vidaza, you're treated along the lines knowing that that was your diagnosis. Now, you may be on therapy with Azacitidine for like six months and you no longer need transfusions and you're feeling fine, but you still carry the label of the initial diagnoses.

Q2: And does your label still include that score that you're intermediate that you stay intermediate?

Jean Ridgeway: It does because what the IPSS score is it's the international scoring system and so what it… but what it's designed to do, that's not a diagnosis. That's really to help the clinician and you to understand the expectations of what usually happens with that subtype.

Q2: Okay, but it isn't like staging in breast cancer where they say, "Oh, well, she started out at stage two, but now she's at stage four." You don't move like that. There isn't any equivalent in MDS.

Jean Ridgeway: The answer to that is sort of. They will never give you… They'll never turn the clock backwards. So, say you're an RAEB2 and you're getting transfusions. You stopped being transfusion dependent. So oftentimes, the physician will document RAEB2, on treatment, no longer needing transfusions, but what we know about the more aggressive types of MDS is that the natural history of the disease is that about 20 percent of people can evolve to acute leukemia which is treated differently than Myelodysplastic Syndrome and so if you progress and things get worse then they'll change your label. Then they may say for people who are unfortunate enough to progress to leukemia, it'll say acute myeloid leukemia evolving from Myelodysplastic Syndrome. So, that's when the label change can happen. Does that make sense?

Q2: Yeah, but even if you're at the end you're still going to be an intermediate.

Jean Ridgeway: So, the risk is always done initially to help categorize and predict potentially the tempo of your disease and then we don't rescore people. So when Dr. Greenberg's study was done that the IPSS scoring system. So in 1997, that's when that paper came out. So what that scoring system did was it looked backwards at 800 patients who had Myelodysplastic Syndrome and at that point in time they really didn't have a good understanding of what made some MDSs more aggressive than others and so when they looked through the data they wanted to see is it male, is it female, do people have diabetes? What is it? What were the characteristics that they could glean and be able to come up with something that was relatively universally adaptable to people. Nowadays… So, that paper is almost 20 years old. Right. Nineteen ninety-seven was when it was published. So, that data you know came from before that. So, maybe the data is 30 years old now for some of those patients. So, some of the criticisms of that scoring system is that people were never treated and so when we look at are you a low risk, an intermediate 1, 2 or a high risk and then it gives that survival, but those were patients who never got treated. So, they were followed, but there was no treatment. There was blood transfusions and maybe growth factors, red cell growth factor, white… but it was basically people who didn't have any treatment options. So nowadays, the IPSS-R, the revised one, what it begins to look at is it recognizes that the cytogenetic abnormalities help us more to understand how indolent or how aggressive the disease will be and then it also factors in, you know, do you get blood transfusions or not

because transfusions really impact overall health and survival and so and I'm sure like that came out like three years ago. I'm sure it will be revised again as well as we understand things.

Q2: As they learn more.

Q3: And there really is no treatment for the disease except for…

Jean Ridgeway: Azacitidine. Hypomethylators.

Q2: Transfusion.

Q3: Not transfusions, but…

Jean Ridgeway: Transplant.

Q2: Transplant.

Q3: Transplants.

Jean Ridgeway: You mean cure. Is there a cure for the disease?

Q3: Is there a treatment for the disease that leads to a cure? There isn't.

Jean Ridgeway: So, the treatments in MDS actually what they tend to do is to slow down the progression of the disease. So, what you want to do is avoid the acceleration into leukemia. So, people who have what's the… some people will… used to call MDS preleukemia and you're going to say why did they do that? Well because in the world of pathology, the number of blasts in the bone marrow, okay, that's the diagnostic criteria. So, 20 years ago they said if you had 30 percent blasts or greater you had acute leukemia. Now, they say 20 percent because the difference between 20 and 30, the diseases behave relatively identically. You know, you have leukemia and there's two different classifications. There's the older class… the first classification system which was called the FAB, French, American and British and that's where the RAEB, that's where all that came from. Now, we have the World Health Organization and they're further defining and I will tell you that there is an update coming within the next 12 months that will be out from the World Health Organization further characterizing many diseases including Myelodysplastic Syndrome. So, there's even more information that will be added into the subtypes to further define them. A lot of them are molecular testing and cytogenetic. So, is there a cure? So, what we often hear is that the only hope for cure is a stem cell transplant. Right? But stem cell transplant is not… it's not a benign therapy. It's a very aggressive therapy in that 1) you get high doses of chemotherapy and so you will have all the potential side effects of that. Right? And then 2) in order for transplant to be successful, enough chemotherapy is given to eliminate hopefully all vestiges of the MDS clone. Clone simply means one cell looks

like another looks like another. So to get rid of the MDS and then allow the new stem cells to repopulate the bone marrow, but in order to do that we have to give people immunosuppression drugs, which allows the person to accept the graft. So when you get the stem cells, it's called getting a graft. You're not really grafting a piece of skin. What you're getting is an infusion of these stem cells. It looks like a blood transfusions honestly, but it's only these selected mother cells called the stem cells and so that's… it's fraught with difficulties because people can reject the graft. People can get these very unusual life threatening infections that are difficult to control and people die from the process of transplants.

Q3: The person I talked to in Wash. U said that there's probably 40 percent in the older age group that won't make it.

Jean Ridgeway: Forty percent that will make it?

Q3: Won't.

Jean Ridgeway: Won't make it. I agree. If you're over the age of 50, probably four out of 10 do not survive the first year after transplant. So, it becomes risk and benefit. Am I going to be the six and 10? Am I going to be the four in 10? And clinicians then have developed a number of different categories that help us understand who will do better in transplant. Can they… being up to the age of 75, centers across the country are doing transplants. So, the center that I work at actually we're trying to specialize in doing these transplants for "older patients." So, we like people who over 60. They present a unique set of challenges, but the fastest growing segment in our population are a) people over the age of 80, but people in 70s and 60s aren't far behind. That's just the demographics of our country and so…

Q3: And that's really where most of the disease is.

Jean Ridgeway: That's right. Yeah. Many. We do… I will tell you that we have people in their 30s. We've had a few people in their 20s and 40s, 50s. It's…

Q3: But the majority…

Jean Ridgeway: The majority can be, right, and then the other piece is although transplant may pose a cure, you have to look at the other illnesses people may come to transplant with. Some people at 70 are robust and healthy. Other people have lots of other issues. They've had heart attacks. They have diabetes that they may already peripheral neuropathy. They could have heart disease. They could emphysema. I mean, the sky's the limit and when do people mostly get those chronic diseases? When you're over 60. So, you kind of have the double whammy of is this really possible? So, I think it is possible, but when you look at who falls into that category, it's a small subset and the risks of going through the transplant, are… they're high and people want to

do know would I do this or shouldn't I do this? Some people will say I'll do anything for another day.

Q3: Everything that I've heard so far about all these studies that are going on are to extend. There doesn't seem to be anything going on that's going to fix.

Jean Ridgeway: So, you have to look at the cause of the disease is the stem cell abnormality. So when our blood gets created… let me go forward a little bit and… We talked about this a little bit, but let me just show you this. So, when our blood cells are created, they're created inside the bone marrow, okay, and that's called a stem cell, a hematopoietic stem cell. That's just a fancy word saying a blood cell and then because of different influences in our bodies both cytokines and hormones, it makes a decision and it either becomes the family of the lymphoid cells or the family of the myeloid cells, but when you look at the disease of MDS, the error is all the way at the very beginning in the hematopoietic stem cell. So, that very first cell is where the error is. So when you think about how do you cure this disease? We have no idea what really are the series of causative effects that someone has the propensity to then develop the disease. That's an unknown at this point in time. We don't know what causes it. If we knew what caused it then we would certainly say well, don't do X, Y and Z, but we know that the error then occurs in the stem cell. So, the natural "if you think about what's the cure," the cure is to give you a new healthy stem cell and we do that by getting rid of yours and giving you somebody's that are new. That's the potential cure and I have lots of patients who are cured and lots of patients who have MDS in their 40s, 50s, 60s, 70… We have a gentlemen who's coming up on his one year anniversary, a physician, 70 years old. Very robust guy. You'd think he's 55. He looks great. He's done wonderful. No other illnesses. Meticulous health. Good… in shape, all the good things. Never a smoker, never a drinker and so what's the cure? The cure is to fix the stem cell by either a) identifying the causes for disruption of b) giving you a new one. We have yet to have the science sufficient enough to say okay, we know what the genetic abnormality is in the stem cell. How can we insert a gene to correct that abnormality? We're just not there yet. So for now, what we have to offer patients in 2015 is…

Q3: Well, is anybody working on that?

Jean Ridgeway: Sure, but it's decades away.

Q3: Why.

Jean Ridgeway: That's how long it takes. It takes a long time.

Q4: Is it because of the funds or is it because…?

Jean Ridgeway: They just haven't found it. They haven't identified the genes that do it.

Q3: How many genes are in that…?

Jean Ridgeway: In the stem cell? All of…

Q3: No. How many genes are in your bone marrow?

Jean Ridgeway: So, our DNA has all of our genetic material.

Q3: There's something wrong with the DNA in the…

Jean Ridgeway: In the stem cell.

Q3: No. There's something wrong with the DNA in the bone marrow that is creating the defective stem cell.

Jean Ridgeway: So, some people ascribe to the theory that it's the like the soil… like the bone marrow is the soil and the stem cells are the seeds. So, some people say that there's an error… there's something wrong with the soil, so you can't grow good crops or something's wrong with the seed or something's wrong with both of them and people have yet… we have yet to really identify what's the bigger culprit, but when we look at therapies like 5-Azacitidine or Lenalidomide with these treatments that people are potentially can get and benefit from. They do a couple things. Lenalidomide works in the soil. So, it works in the bone marrow micro environment amidst all the different complicated mechanisms in there to change the milieu of the soil. That's what Lenalidomide does. That's a very simplistic description. 5-Azacitidine works on the seed. So, it works in the DNA because in DNA you have methyl groups and that drug is a hypomethylator or it blocks the methyl groups in the promoter region of the gene. So in genes, there's an engine that drives the replication of the DNA and that's called the promoter region. So in the promoter region, they have too many methyl groups and that helps block that and changes the look of the DNA, but it doesn't change the promoter group. It just… It's a therapy to stop it. So, you're absolutely right how do you cure it? All I can tell you is that they're working on both situations, the soil and the seed are both being worked on and therapies that are offered to paints look at treating one if not both of those areas to help improve the natural consequences of the disease. Make sense?

Q5: So, actually the stem cell or the bone marrow transplant that would be kind of the last thing… I mean, that's your last resort basically as far as if your medication is not working. I mean, you can only... I mean, if the medication stops working you either go in for a stem cell transplant or you just wait until you die.

Jean Ridgeway: Or you try another therapy.

Q5: That's what I'm saying though. Actually, I would say the bone marrow transplant would kind of be the last thing that we would probably try. I mean, if everything's working well even some of the doctors kind of say you don't want to wait till you get really sick to try to do a transplant because then… I mean, you're already sicker and then you got to go through this chemotherapy and so that's not good, but you don't want to go into it too soon either because it's so drastic.

Jean Ridgeway: Right. Remember he showed… Dr. K showed a grid and it said when do people get transplant? People with early stage disease should get transplanted later, but with people with very aggressive disease should get transplanted sooner and part of what we know is that people who have very aggressive disease are just a step away perhaps from having acute leukemia. One of the most important things about transplant is that people need to be in remission in order for transplant to be effective and we have patients… As providers we discuss our patients at conferences and we get input from all of our colleagues and if someone is not in remission even if they have a donor you know that the soil and the seed, it's not going to be cured by giving them a transplant and they may have six or nine months of remission, but you still have the vestiges of malignancy even with the new cells and that person will probably relapse within six to 12 months.

Q5: What do you mean by remission?

Jean Ridgeway: Remission. So…

Q5: So, I her that talked about but I…

Jean Ridgeway: So when people are in remission in the framework... when people talk about remission in Myelodysplastic Syndrome, it's different than if you're talking about it say in lymphoma or breast cancer. Breast cancer there may be a malignant tumor. The tumor's removed, maybe the people get chemotherapy. They get reimaged and there's nothing there. Okay. Then that's remission, but in Myelodysplastic Syndrome remission means that your blood counts are normal without any help. So, you're not getting EPO, you're not getting Neupogen, you're not getting transfusions and all those blood counts are normal. So, normal white count, normal hemoglobin, normal platelets and the bone marrow is also normal. You have less than five percent blasts, you have no dysplasia, you have no chromosomal abnormalities. So, everything is normal. That's what remission is. Everything is normal. Now, sometimes people go into an incomplete remission. So, everything may normalize except their platelets. Their platelets may be 50,000. So, that's an income remission, but absolute true remission in MDS is across the board normal.

Q5: And how do you get to that?

Jean Ridgeway: How do you get to that? Well, you get treatments, sometimes 5-Azacitidine or Decitabine and it's recommended that get four to six cycles before they do a bone marrow to assess for their status. I mean, you can watch people's blood counts as you're going through the treatment. Most of the time when people start Azacitidine, their counts are reflecting that they need treatment. Their white count may be low, they may be anemic and in general and I'll show you some pictures oftentimes blood counts get worse before they get better and you can think about it, again, if you look at the soil and seed analogy, if you have a garden and you're tending it and you're very regular about it, that's great and then you go away on vacation and nobody's watered your garden and no one's weeded your garden when you come back the weeds have really… they're very opportunistic and they kind of take over. So, what the Azacitidine is going to do is you look at the bad cells as the weeds and you start pulling them out. So if I spend the afternoon weeding my garden, my normal plants are still there, but they're looking very scrawny. They have a root system, but they didn't get adequate nutrition because they were crowded out by… the sun was crowded out, the nutrients were crowded out and so as you start to treat someone you're removing the malignant weeds and then the new… the remaining plants are going to have to grow, but they're going to have to have… they'll have some difficulty as they try to regain the normal soil as the soil changes and start developing normally. So, oftentimes what we'll see is a worsening in counts the first four to eight weeks and then an improvement of counts as you get rid of the malignant cells.

Q5: Okay but that... So, what you're talking about is the chemo. People have before they have the…?

Jean Ridgeway: No, I'm talking about Vidaza. Even Vidaza. Same thing because Vidaza is a… it's a smarter form of chemotherapy. It's still categorized as chemotherapy.

Q5: But you could stay on it.

Jean Ridgeway: You can stay on it. I have patients on it for five, six, seven years. People who started off transfusion dependent are no longer transfusion dependent.

Q5: So, why don't they just begin with that instead of other things?

Jean Ridgeway: Well, because it's very individualized. If somebody has 5Q-, you don't start them off on Azacitidine. You start them off on Lenalidomide. If somebody has mild anemia but no real need for anything else starting off with Epogen is what you should do because it's not one size fits all. It's here's all the characteristics. What's your subtype? What's your IPSS risk group? What kind of low blood counts are you experiencing? Maybe none. For many people who get diagnosed with a really low risk MDS, the doctor says come back in a month or come back in three months and then we'll see you and you kind of walk out the door a little stunned but perhaps that's what needs to be done. There's nothing to… where do you begin treatment and that's some of the questions when you look at the studies that are going to be done here with low

risk patients when do you really institute therapy and currently in 2015 what we're saying is if people have symptoms like you're symptomatic from the anemia, maybe you have heart palpitations, headaches, shortness of breath, fatigue that interferes with you're being able to do what you want to do then the provider will say, "Okay. It's time to start therapy," and this is because of all these other factors here's what we'll start with.

Q5: Because I know I went a year… I went more than a year, almost two years and we watched and then it started slipping a little lower and then she said…

Jean Ridgeway: Time to start.

Q6: How often should you have a bone marrow test?

Jean Ridgeway: It all depends. If you're a low risk, if you're a high risk, if your blood counts are stable, if your blood counts are dropping. So, it really depends on what's going on. Certainly you need one at diagnosis and then if you're starting on a therapy. Say you're starting on Azacitidine, many physicians will say in the community that you don't need to have a bone marrow in like four to six months if your blood counts are beginning to improve. If your blood counts in six months are identical from when you start the Azacitidine therapy most providers would say let's do one and kind of see where you're at. Are you the same, are you better or are you worse? So, it's…

Q6: What's the difference between Procrit and Aranesp?

Jean Ridgeway: Aranesp?

Q6: Yes.

Jean Ridgeway: So, one is the method of delivery. One of them is a fat soluble molecule and so it has longer efficacy. So, the Aranesp can be given… No, the Aranesp and the Erythropoietin are the same. Darbepoetin is another medication and that one is a fat soluble. So, Aranesp is Epogen, erythropoietin. It's the brand name versus the generic name.

Q6: Okay. So, Procrit and… are similar.

Jean Ridgeway: They're the same.

Q6: They're the same.

Jean Ridgeway: They're bioequivalent with a different label and there's also a medicine called Darbepoetin which is a long acting. You can get that injection every three months, but many

insurances who are paying for those injections will say they pay for Epogen or Darbepoetin, but they don't pay for the long acting. So, times there's the gatekeeper.

Q7: I know my (inaudible 29:26) they said they could raise that drug.

Jean Ridgeway: They can raise the dose.

Q7: Raise the dose.

Jean Ridgeway: Up to 80,000 units.

Q7: Huh?

Jean Ridgeway: UP to 80,000 units.

Q7: I'm getting 200 now, but…

Jean Ridgeway: Yeah. You're on the longer acting one. So, it's kind of… It's like metric and English system, there's meters and inches. So, we have to know what the… how you equilibrate them and make them say the same thing.

Q7: But he said it could go up. He could raise it if I needed to.

Jean Ridgeway: Yup. You can and what we also know about any of the red blood cell… so, that's a red blood cell stimulating hormone. You can ask Lance Armstrong.

Q7: Oh, that's what he did.

Q8: Is there any indication as to the length that you can use the Procrit? Like I started six months ago and I started a year ago at 20, six months ago it went to 40. Now, and used to do it every two weeks. Now, we're doing it every week. So, we're really getting twice as much. Is that an indication it's not working? That it is not as effective as it used to be?

Jean Ridgeway: So, Erythropoietin works on a hormone in your body. So, on your adrenal glands we normally secrete erythropoietin and from our bone marrow as well and it's one of the ways that our body creates hemoglobin, but it's not the only way and for patients who have MDS, if you begin to have very high doses of erythropoietin and you're not getting benefit from it, it's not maintaining your hemoglobin then that's usually… it can be a sign to try something else. You can think about it as your body only needs so much erythropoietin. So if I tried to pour water into my full bottle, it's just going to spill over. So, it's really… it doesn't benefit, but if your bottle is half full then putting some in is going to give you benefit, but there comes a point

in time where adding erythropoietin is not giving you the benefit because that's not the problem any longer. Now, the problem is that your bone marrow more than likely is beginning to fatigue.

Q8: So, would you have your bone marrow at that point?

Jean Ridgeway: I think that's a good time to get your bone marrow checked.

Q8: Thank you.

Jean Ridgeway: Anything else? I'll go backwards a little bit.

So, Dr. K talked about this. What is it? So, the M in Myelodysplastic Syndrome means myeloid. So, the stem cell either goes to the lymphoid family or the myeloid family and the D is dysplastic which means an abnormal shape and I'm not a pathologist although I have friends that are, but that indicates just some very unusually shaped cell and why is that important? If you think about when we drive a car when we're in a car, we're assuming that the wheels are round. If you have a flat spot on your wheel your wheel still works, but it really doesn't work as well and is it going to impact on the way your car functions? (Agreement sound) It will and it's the same thing with the cells. The abnormality in the shape disallows them from doing their job properly. So, the job of the red cell is to carry oxygen to our bodies. We live on oxygen. That's just the name of the game and it can't do that very effectively when it doesn't carry the right shape and hematopoiesis is a big word that just means the development of blood cells and just like my garden that I didn't tend in the summer when you begin to allow… when the bad cells begin to crowd out all the good cells you start having cytopenias because the weeds in my garden are just like the weeds in my bone marrow in that they begin to suppress the normal cells and that's when you start seeing changes in blood counts. So, you have cytopenias or low blood counts and then, again, what's the risk of this? Some people can develop leukemia and as the disease progresses what can happen is that the bone marrow function can decline. So if you're getting Aranesp and you're getting a little bit more and you've been doing it for a bit and it doesn't seem to be working as well, it's time to take a look and see what's going on inside because the blood counts, unfortunately when we draw them from the vein, there's not a one to one correlation of what's going on inside the bone marrow which is why you have to do the exam.

Alright. So, there's the lymphoid cells and then there's the myeloid cells and what should be out in our blood all the normal cells that are created from the myeloid stem cell are neutrophils. People talk about a white blood cell count. There are five major types of white blood cells and the neutrophils should be about 80 percent of it. They fight bacterial infections. So when you look at your blood count, it'll say your CBC, stands for complete blood count, and the three major pieces that have meaning, the WBC, white blood cell count, and within that the ANC, the absolute neutrophil count. How many of your white blood cells are neutrophils. So, it should be 80 percent. Sometimes in MDS the absolute neutrophil account is really… it drops and you have more lymphocytes than neutrophils and then these are some other cells, basaphil and eosinophils,

macrophages, platelets are the other thing you want to look at and then red cells or hemoglobin is what we look at in the CBC. So, white blood cell count with the… paying attention to the absolute neutrophil count, platelets and then your hemoglobin.

So in MDS, we have defects in that marrow environment and then we have abnormal blood development and so what happens what that happens? So, the normal ones kind of like go to the side and there are all these factors that really are being studied, but then we have these immature cells. So, immature cells as a stem cell grows up by the time it goes from stem cell to mature cell there's a process and the baby cells are called blast cells. Those are immature cells. It's normal to have them because it's part of normal maturity, but all good little babies need to go to college and grow up and get a job and that's what our blood cells should do. They should grow up and be functioning members out in our blood doing their job, but they get arrested. They get stopped. They stop growing and they're blast cells and so the interesting thing about malignant cells is that they become immortalized. So, they don't die. Normal cells are very interesting. They live their useful life and then they die and our body replaces them and there's basically this one to one replacement. So, that's why we all don't like bleed to death by the time we're one because our cells just replace and as we grow bigger then they just replace, but these immature cells continue to multiply without dying. There's no natural cell death and so when we see the accumulation of them in the bone marrow, it's because they're immortalized and when you think about how that happens when the cell replicates or duplicates usually one cell just replaced itself. Well with malignancies, one cell becomes two cells and then two cells become four cells and four cells become 16, become 32. So, they double. So, we talk about a doubling time and if you take just one cell and you double it 30 times how many cells do you think that makes?

Q8: (inaudible 37:54)

Jean Ridgeway: Over a million. So in 30 doublings, you have a million cells from one cell that should have died and just replaced itself. So, we start seeing the accumulation of the blast cells in the bone marrow crowding out the other cells and there's nothing to… They're not naturally programmed to die. So, they start accumulating and crowding out the other cells. So, those are those immature cells and that's when we start seeing then our normal cells are being crowded and our cells… when we do the bone marrow you might read in the report that it says something called hypercellular. So, we all have cellularity in our bone marrow and it's a simple equation. You take 100 percent and you minus your age and that should be your cellularity. So, it changes with time and if you have more than is expected, we say it's hypercellular like hyperactive children are pretty active, hyperactive bone marrows are very active and there's usually two reasons for bone marrows to be active. One of them is you may be getting ready for a stem cell transplant or have had like an accident like you lost a loss of blood and your body's got to get busy and replace them or you have an infection and your body's busy, but the other is disease because of that because of doubling, doubling, doubling. So, it's hypercellular and it's a mix of how much available tissue is there to fat really and that's just the bottom line and so you have a

lot of tissue that's very active if you're hypercellular. So, you have a lot of cells in there, but you have blood counts that are very low which kind of seems a little odd, but that's what happens.

So, how is MDS diagnosed? Well, some of you in this room talked about that you needed surgery because no good cardiologist is going to touch a patient or his lawyer unless he checks your CBC. So, you get a CBC and through the decades more and more primary care doctors are beginning to recognize symptoms of anemia as tiredness. There are some providers that say, "Oh, you know, you're a 60 year old woman. You're post-menopausal. Of course, you're tired." Whatever. So, they disregard it, but so it can get picked up by a primary care doctor who does a CBC and pays attention why are you anemic? It's not normal to be anemic. That's really not normal physiology. There's many types of anemia. There's iron deficiency. People in this room are not iron deficient I doubt. If anything when you get a transfusion you get all this iron. You can have some vitamin deficiencies. So, some of those fixable anemias that Dr. K talked about that's why. Some people get diagnosed with MDS because they're symptomatic, they're anemic and then they go see medical attention. Some people are very ill by the time they get diagnosed and they may have very, very aggressive disease that is presenting itself like leukemia because it's easy to disregard symptoms. You're short of breath, you're tired. Other people can get diagnosed because of their low white cells. They get infections. So perhaps, they have an ear infection then they get pneumonia then they get another pneumonia and then they have some other infection like a gallbladder infection and that really if you think about it, it's not normal. People get pneumonia. Yeah. People get an ear infection, whatever, but to have repetitive infections is usually going to trigger to the primary care doctor we better draw a CBC and see. So, their white cells can be very low and they're neutropenic and that's how they get diagnosed. So, lots of different ways, but eventually you all meet your friends, the hematologists and usually it says hematology oncology and people are convinced they have been sent to the wrong doctor because to get the phone call of you need to come back. We found these abnormalities in your blood counts. I mean, that's a phone call where it doesn't compute. It's kind of like watching a real in TV, but you can't hear it. So, that's what happens and then we talked about the bone marrow and all those things that need to be done and then some other things that get done is we do definitely test people's thyroid function. We do lose that a bit as we age. Testosterone drops as men age and we have to just look at organ profiles as well, but all that taken together then helps us get the diagnosis of MDS and like I said before, you should really own a copy of your pathology and know your subtype and then know your score and you can do your own score on the website.

And so this is a busy slide, but it basically says that there's a lot of different ways to classify Myelodysplastic Syndrome. So 1960, 60 cases then in the early '70s, the first classification system came about and one of the gentleman who the physicians that was really responsible for the MDS Foundation to get organized, John Bennett, was on the group. FAB stands for French, American and British. So even back in the '60s and '70s, they recognized as a professional group that they were all seeing the same thing, but what were they seeing and how can we put consistency and standardization to this nomenclature so that we can begin to understand it? So,

that's what FAB is. So, the French, American and British hematologists got together and said let's get some substance to it. So, they talked about five major subtypes. Four of the five revolve around anemia. Eighty five percent of all MDS patients have issues with anemia because the red cell is so involved. So, there' refractory anemia and then the ring sideroblast we talked a little bit about that and then excess blasts. How many blasts are too many to have? Over five. That's too many and they categorize them into RAEB1 or 2. That just stands for refractory anemia of excess blasts and then in the early… in the late '90s, the WHO, the World Health Organization, began to look at that information with new scientific information and start adding in cytogenetics and recognizing some of these MDSs behave differently than others. Some of them… People can have really high white counts where their white count is 200,000. So, it behaves differently and then someone has a low count. Anyway so and then they just talk about how many blasts and all these dysplasias. So, there's kind of a lot that goes into it, but and it continues to evolve.

So, we talked about this already, the IPSS and the IPSS-R and it really helps your doctor understand what your risk and prognosis and it really becomes the cornerstone of deciding what are we going to do about treatment? What treatment is appropriate for you because everyone is different and just because the diagnosis says Myelodysplastic Syndrome there's a lot of different… That looks a lot of different ways. I mean, everybody… the folks in this room who are affected with it everyone is different. You're not the same. We're not going to do the same thing for (Attendee) as we do for (Attendee) as we do for (Attendee). We're just not going to do that. We have to look into all these other factors.

This is the website if you wanted to go on it then you just go ahead and you can put it on your iPhone. I don't know if anybody is savvy with the iPhone. I have to have it on my phone because I do this in clinic a couple times a day.

We talked about what do we know about MDS? We know that the largest group of folks that get affected are as we age. So in the 70s. It is a malignancy and it's the only potential… See that word how it's qualified, potential cure, but the leading cause of what do people fail from? People fail from the disease itself about 80 percent or complications of the MDS on some prior existing illnesses. So people who have preexisting heart disease like they've had a bypass. So, they've had a major heart attack. They have damage to their heart already. Those people don't necessarily tolerate having a lower hemoglobin threshold than someone who hasn't had that because they have less tissue in their heart that's really available to them. So, they could have more problems.

And what do we know that risk stratify treatments. That basically says let's look at all of your characteristics and pick the best treatment for you. That's what a risk stratified treatment is and things are individual. When do we start treatment? When do we start it? We start it when people basically have indications that they need treatment. So, what's going on with your transfusions? Do you get one transfusion a month? Do you get one transfusion a week? Do you get one transfusion twice a week? I have a gal, she's been on treatment. She has a lot of illnesses that

coincide to her MDS. She's in her late 60s. She does get treated. Her platelets she lives with a platelet count that's under 10,000 and she has for two years. She's had no major bleeding episodes. So, that's part of that accommodation, people living with the new normal, but she's a very poor transplant candidate. She continues on treatment with Azacitidine. I think she's had 28 treatments and we started treatment with her when her anemia really started to impact her quality of life. She has very based emphysema. She smoked like four packs of cigarettes a day for 40 years. No, she don't smoke anymore. She doesn't smoke anymore, but some things can't be reversed. When you do damage to your lungs then you do… and so… but that's who she is and she watches grandchildren and she drives a car. She comes to clinic, but she gets transfused… she gets transfused still every week. She gets one or two units of blood and she's okay with that and we continue to do therapy. It doesn't cure her disease, but it does keep her disease stable and she has a good quality of life. She doesn't live in the hospital. She's like never hospitalized.

So, and then when we look at… So, all those things need to be considered Now, something we really didn't talk about was something called secondary MDS. See how it says primary versus secondary MDS? So, secondary MDS sometimes is called therapy related MDS. So, people survive malignancies. Men survive prostate cancer. Women survive breast cancer. People survive lymphoma, multiple myeloma, but to survive those treatments they're often given pretty high doses of chemotherapy and/or radiation and it can damage the DNA further to three to five to seven years later they may develop MDS even though they're cured of their breast cancer and so we call that a secondary or a therapy related. Now, those people are just like you, but they don't get scored in the IPSS scoring system because they're therapy related. Our largest group of cancer survivors actually is Hodgkin's disease. So, Hodgkin's lymphoma is usually a disease of younger people. I saw three people on Friday, 26, 28 and 29, all three women all going through Hodgkin's therapy, cancer… they get chemotherapy every other week for 16 weeks. So, that has changed over time some of the drugs, but we're seeing more and more Hodgkin's people survive. Twenty-five – 30 years later they have developed MDS in their 50s. And we treat them… We go through the same series of individualized treatments, how old are you? Are you a potential transplant candidate? How should we treat you? What else is going on? So, that's a whole other layer of people who have MDS are these cancer survivors and they call them therapy related and then we make treatment selection is what really is going on and what are all... I call it the disease signature. When you think about what is your disease all those things are based in it.

So, we talked somewhat of this. What kind of things are available? So, all hail the potential cure for transplant. We'll kind of put that to the side, but then there are what we consider in America supportive care. In Europe they call it active therapy. So if you get blood transfusions and you get shots of EPO or Neupogen, if you live in Europe they say you're undergoing active treatment and I do agree with them because it's doing something rather than doing nothing and then there's a number of medications. Lenalidomide or Revlimid is a pill that's taken. Vidaza is the trade name. Azacitidine, 5-Azacitdine is the compound name and that came out in 2004. It's an injection and it can be given as injections like insulin or it can be administered intravenously. For some patient who already get transfusions and they have a portacath, getting the infusion, people

would rather get the infusion than get the shots because it's at least two shots a day for five to seven days every month. It all depends. Some people are, they're like I just want to get in and get out and when you look at how much time you spend in clinic, chemotherapy is expensive. So first of all, the pharmacist does not make up your drug until you're there and you've been cleared. So, it's not like why can't this go faster? Well, that's just not how it's done. So, you get there, you check in and you do all the stuff, but that can be an injection which is quick. You get in the chair, they do the triple check. You show them your belly or your arm and they give you a couple shots and you're out the door. Infusions take longer. If you don't have a port, you have to start an IV. You sit there longer. It's like a 20 minute infusion. Dacogen or Decitabine is another drug. It's similar to Azacitidine, but it's a few molecules different. That's only infusion and then there's some chemo as out there and then again clinical trials.

D9: Do they ever expect maybe that Vidaza could be in pill form?

Jean Ridgeway: It's in right now in clinical trials. We have a clinical trial open with oral Azacitidine and it's working just fine. People are doing well.

D9: How long do you think that might before (inaudible 53:25).

Jean Ridgeway: I think… they'll… so, they have to get enough people in the study and then they have to analyze the data and then it goes to the FDA. Probably a couple years. So, people want pills instead of shots, but it's interesting that when people take pills sometimes they don't take the pill. There's some other leukemias that require you to take a pill a day and people don't take it and they're usually horrifically expensive. Like I think Revlimid is… the true cost of the medication now… it all depends like when you look at your insurance, I would encourage all of you to really take a look at your insurance and get a supplement like a Part D supplement to make sure that your prescription drugs can be covered because all you have to do is get one expensive drug and your hair will fall out. So, I think Revlimid is $3,500 a month if you don't have any assistance. So, it all depends on what your insurance company is paying and the other option when people have… like who can afford that? Nobody. So, most companies have what's called patient assistance programs where they provide drug at a greatly reduced cost like maybe $30 to patients. All of the big pharmaceutical companies have that because otherwise they couldn't do business. So, they're out there.

So, what else is out there? There's some other drugs out there in clinical trials. The one drug that he was talking about this morning… that they talked at the big meeting the Rigosertib. That was… the results of that were okay and they're bringing it forward into more clinical trials before the FDA says okay, we'll approve it in this indication. So, when the FDA gives a drug company an indication, they basically say you can use drug X if the person has disease X1. So, I can use Lenalidomide if I have 5Q-, but if I don't then they're going to say no, you can't use that and then your insurance company will say and we're definitely not going to pay for it if you're using it without the indication. Anyway, this is an older list and when you look at what are they

targeting, we talked about like the soil or the seed. That's exactly what this list represents. Histone deacetylase inhibitors, the HDAC, the Panobinostat one at the bottom. That targets the DNA. It helps change the characteristics of the DNA. The PI31 kinase, that's a soil changer. So, I mean, there is a lot going on. Nothing's been shown to be like the winner. No magic bullet yet, but they're working on it. So, there is a lot of research and if you like to go on the Internet, I think probably looking at the MDS website because that will link you to the National Cancer Institute. What's a valid trial? That's where you want to look.

Other things that we think about. A big key point is that all active treatments for MDS require time to work. If you're on Azacitidine or Decitabine you have to allow for four to six weeks. If you're on Epogen, actually it's recommended to be on for at least 12 weeks before you say this dose isn't working or we need to do something else and the other thing for Epogen is that red cells require certain nutrients. They require folate, folic acid. So, make sure you're taking a vitamin that has high levels of folic acid in it or folate as well as B6 and B12. So, those are other building blocks of the red blood cells and then we talked a little bit about blood counts getting worse before they get better and then talking to your provider. If you start on a treatment and you start having side effects, you need to pick up the telephone and call your doctor. So, if you say I'm having mouth sores or I can't swallow or I have this funny looking rash, you really need to call your doctor. I would say especially as we look at November, two things that everybody in this room should think about is to make sure that you've gotten your flu shot and the people you live with got their flu shot because infection still is… it can be difficult for people and then good handwashing. So, make sure you're washing your hands. Pack some Purell and do good handwashing because to protect yourself from infection the thing that's the best thing to do is just wash your hands. Soap and water is fine if you're someplace. If you go to the store, wipe off the bar and go ahead and do that.

So, this is just that like picture of why does it take so long. So, this is what's happening inside the bone marrow. So, this is supposed to give you an insider's look of what's going on in the bone marrow as the blood counts drop as the MDS progresses because they're crowded out by the abnormal cells and so we're going to watch somebody's neutrophils. So, the graph in the right hand side. So, absolute neutrophil count this person already is kind of neutropenic and what do you see? The line goes down and then it begins to slowly go up to a better level. So, that first bar tells us that there are a lot of abnormal cells. So, the big purply cells with the lobules inside, those are blast cells. So, you want to get rid of those and the red disks, those are hemoglobin cells. So as you start cleaning out the bone marrow, you see a drop in the blood counts and that's expected, but if it begins to recover then normal cells and then you should start seeing a rise. So, you can see a difference in the pictures. There are not as many cells as the one to the left, but they're starting to look a little bit better until you get normal cells back. So, everything on the right-hand side really looks relatively normal and then you see the blood counts return and during this time period that's taking a good… this person this is an actual person. So, this is weak. So, up to six weeks the person's counts are going down, down, down. It's really not till about week 11 or three months later that this person's blood counts are leveling out and that's the

time when people start saying okay we can… people's blood counts tell you you don't have to come in as often, you don't need transfusions, you don't Aranesp, but it's that low point that people are… they don't feel great. When your blood counts are low, most people don't feel well. They feel cranky.

So, let's see.

Time. Again, we talked about this before and their strategy is getting through those initial cycles of chemo. So at our center when someone starts treatment we see them. We recommend starting treatment. We're going to see you in a week and we're going to recheck your blood counts. So, that first month we will see you every week just to check you blood count, just to see how you're doing, making sure that everything is okay. There are certain people because of risk factors do get put on some prophylactic antibiotics like when do you take antibiotics if your blood count is low. The studies have shown us that in general it's not a good idea to put everybody on prophylactic antibiotics. That would be like taking an Augmentin or a Cipro every day because then what we add to is the generation of super bugs that no longer are effective to antibiotics. So, there is a place for it, but again it's individualized. So, we would see you and if you do well during the first four weeks then the next time around we may not see you the second week. We may see you the week after and I would say, too, if you are on treatment, learn how to contact your doctor or your nurse practitioner. Get their card. Get their E-mail. I'm an E-mail person. I never am at my desk. So if you want something, E-mail me I'll answer sometime during the day or after the day. If it's urgent, page them. If you ever have a fever, 100.5 or greater you need to call. You know you're going to need to be seen or admitted or something, but don't wait.

Q10: There's also talk that my dentist said I need to know from your doctor about whether or not you need to be on antibiotics prior to getting your teeth cleaned.

Jean Ridgeway: So, the rule of thumb and the recommendation from the American Dental Association is if you have an implanted port you should be prophylactic Amoxicillin. You take two grams the night before and two grams the morning of if they're going to do a cleaning. If you're going for a regular exam, you're okay and for my patients who are neutropenic, I don't require them to go on antibiotics if they're going for a cleaning. They need to inform the dentist that like my platelets are low, so I might bleed more. So, just let them know what's going on health wise. Some dentists get a little shy. They're like yeah, I'll call your doctor and then if you look at extractions then you have to do other magical things like give people platelets if they're truly going to get an extraction because that's another way people get diagnosed with MDS is they get a tooth pulled and they never stop bleeding. So, that's just another thing.

Alright. This is just an example of a patient who was on Azacitidine. He happened to be an engineer, so he plotted his own numbers and so he started… so the purple squares are his hemoglobin. The yellow triangles are his platelets and the white blood cells are the darker ones and so you go time from left to right. So, you can see that initially his anemia… So if you look at

what's normal. So, way back here in 2010, he had a relatively normal hemoglobin and not… his platelets were like 80,000. So, that's not normal and a white blood cell count that also is not normal. So, his counts are kind of dropping and then he starts his chemotherapy. So, you can see that he has some variability, but in the long term he gets… it's like a one, two, three, four and then he gets a transplant and then after his transplant really take a jump up because now he's got somebody else's stem cells making all of his blood. Whereas over here first we have to get rid of the bad cells before you can get the transplant. So, that's just an example of somebody who you can see they're up and down and they got worse before they got better, but they did improve especially the platelet counts.

This is somebody who's been on Lenalidomide like (Attendee)'s been on it. She said like eight to 10 years. This person has been on for 10 years and you can see their hemoglobin initially started out at nine and now they went up and they've had some variability in their blood counts. So, the pink is the hemoglobin, a little bit of up and down, but this person's been on it for 10 years and so how long do people stay on it? As long as they benefit and this person's been on it for a long time.

Again, this is somebody who started off low. You can see the up and down. Actually, I went backwards.

Alright. So, what do I do to stay healthy? So, sometimes people have questions about diets. What I would say to you is eat foods that are probably as close to what God created. That's a good diet. Try to eat less processed and more like natural. Wash things that come out of the ground. You don't know who's picking the food. You don't know how clean their hands are. So, make sure things are washed. So, that's what I would say. Continue to walk. You said you're a walker. You should do that. Avoid infection. We talked that. Avoid bleeding. You should do things that you like to do. Some people like to ride bikes, ride horses, drive motorcycles. Make sure that you get enough rest, but remember to balance the rest. Sometimes when we really don't want to do anything, the best thing we could do is get on our two feet and get out the door. Clear your mind. Go for a walk in your neighborhood. Walk down the road just to get outside and take a deep breath. There's lots of resources. The MDS Foundation is a great place for reliable information. Just be careful where you go on the Internet and when you need help, ask for help. If your kids say what can I do? You say could you clean out the gutters? Can you flip the storm windows? Can you clean out the basement? What do you want for Christmas? A cleaning lady. So, make life practical and helpful. What do you need help with? Here's what I need help with and then be a participant. Some people like to know everything. Some people like to know not so much. So, you find what you like and your partner or your family may be the exact opposite of you, but there's enough information out there to make everybody healthy.

Then this is that book that you have and I told you its available online and then there's an online interactive forum that we talked about that already and then in there is if you want to keep track of your own numbers and transfusions. There's a way to do that both in that spiral book and the

book itself and then pages 85 to 91 in the big book are looking at your progress and just kind of useful tools to take to your healthcare provider visits. So, that's where that can be found. If you don't know how to get a hold of the MDS Foundation, all you have to do is look on the back as some of the information here today and that'll give it to you and then Audrey's E-mail is down there and then this is just kind of going through the book itself. It talks about what is MDS? So when you go home, it's always interesting to go to conversations like this and you think you understand it and then you walk out the door and you go, "What did they say?" So, it's all written down. It's in the book. So, how do you understand it, what about quick tips, what about iron overload that we really didn't talk about and then tab number five is really looking at your MDS plan and how to find that and then the Foundation is tab number six and that is the end of what I have to say.

So, questions? I said we'd end at two. I'm a minute and a half late.

Q11: I have a question the hematocrit and I'm probably mispronouncing that.

Jean Ridgeway: Right. Hematocrit. So when you look at your CBC, there's hemoglobin and hematocrit. So, it's always a one to three ratio. So if your hemoglobin is nine, your hematocrit is going to be 27. So, some centers report hematocrit instead of hemoglobin. It's very European to report hematocrit.

Q11: I always feel really bad when mine is low.

Jean Ridgeway: The hematocrit? Well, because then your hemoglobin is low, too.

Q11: So, they just…

Jean Ridgeway: They correlate.

Q11: Okay.

Jean Ridgeway: It's a one to three. So if your hematocrit is 20… if your hematocrit is 18, your hemoglobin is six. That was the last lady I saw yesterday. So, she's getting transfused today; 6.3 she was and she was absolutely fine with that by the way. She's like, "Eh, I'm a little tired." So, she had MDS and she had a transplant and her hemoglobin… she had something called an ABO incompatibility where her blood type and her donor's type are different and so she's changing blood types, but in between time then her blood counts are… her red blood cells are very low. So, she was… Yeah. She was like, "I'm okay." So, it's always a ratio. Other questions?

Q12: The bone marrow donors, so many people still think that to have to give the bone marrow…

Jean Ridgeway: Stem cells?

Q12: Yes, that you still have to go to the hospital and go into the back and do all that stuff. That isn't so anymore.

Jean Ridgeway: No. So, 99 percent of all stem… so now we don't call it bone marrow transplant. We call it stem cell transplant because people get their stem cells. So just like people have stem cells in our bone marrow, how does the donor how do they give it. They get four days of Neupogen shots, the white blood cells shots and that causes the bone marrow to overproduce them and then they get out into the peripheral blood and then they get hooked up to an apheresis machine. So, it's basically an IV in each arm, the blood gets taken out, it gets centrifuged and the machine is smart enough to know the weight of the stem cells which it collects and then the blood gets returned in the other arm. So, it takes about four to five hours and the stem cells are collected. So, there's about… In Europe and for aplastic anemia sometimes they ask donors to go to the operating room to get their stem cells collected. There's no Neupogen and then it's just like doing like myself and the physician we'd be in the operating room and we're doing bone marrow aspirations, about 50 on each side. So, the person's out under general anesthesia.

Q12: So, it's kind of like giving blood, I mean, as far as you donate.

Jean Ridgeway: Right. If you've ever donated platelets it's the same process.

Q12: I never donated platelets, but I've seen it because I get blood but I haven't done…

Jean Ridgeway: It's the same process…

Q12: Okay.

Jean Ridgeway: … with a little bit of a tweak to it.

Q12: That's a good to know for donors because so many people are I don't want to go to the hospital and get that in my back.

Jean Ridgeway: No, that's not the way it is.

Q13: It doesn't hurt some people.

Jean Ridgeway: The people who we've done so very few. In the past 13 years, I've gone to the OR twice to do a stem cell harvest. It's just not done anymore.

Alright. Well, I hope you had your questions answered or at least your understanding increased. Thanks, everyone, for coming especially.