Speakers:
Dr. Stuart Goldberg

Dr. Stuart Goldberg: Hello, everyone. My name is Stuart Goldberg. I'm one of the leukemia doctors at the John Theurer Cancer Center in Hackensack, New Jersey. For those of you not familiar with the East Coast, I live in Manhattan. So, it gives you an idea. We go across that bridge that Governor Christie blocked and for the last, I guess, 10 plus years I've run the MDS Foundation Centers of Excellence. So, you heard a little about that. So, there are numbers of hospitals across the country and actually across the world that have physicians who have had a specific interest in myelodysplasia who do research, had outreach programs, have other something that by meeting certain criteria as the MDS Foundation feels that we should be sort of the advocates from the medical and scientific side. In addition to this meeting because we actually have this MDS Foundation meeting at our center every about two years or so because it rotates around the country. The MDS Foundation also sponsors international meetings and has a big scientific meeting every other year that I've had the fortune to speak at.

Q1: Once a year or more?

Dr. Stuart Goldberg: The international meetings are… well, they're every year but like one year in Europe and one year in the United States.

Audrey Hassan: It's every other year. In the past year it was in Washington DC the first time in many years but next year it will be at the (inaudible 1:40) want Dr. Goldberg (inaudible) and we have more (inaudible) we actually (inaudible).

Dr. Stuart Goldberg: That's geared towards the physicians to try at sort of the cutting edge to try to help us understand the disease and exchange ideas on where we should move the field.

Q2: Professional level.

Dr. Stuart Goldberg: That's the professional level and then I know we had a third world symposium I talked at once to try to educate physicians outside the country. There are also other sources of information. The MDS Foundation especially their website is very nice to download. It has multiple languages which I always find helpful for my patients. There's also another organization. So, the Aplastic Anemia MDS Foundation. It has similar booklets that you can look at and certainly the Leukemia Society is sort of the big umbrella that does all of the blood disorders and so all of these organizations have additional information and I would since unfortunately with myelodysplasia it's sort of one of those common diseases that most doctors don't know very much about and so I heard comments earlier today and I switch my doctor and maybe the care I wasn't getting was up to standards of what it should have been and so we get that realization and there's also a big problem in American medicine and that is where do you go for your doctor. You go to somebody because a neighbor down the street told you that's where

you go. We don't have that transparency of where to go for a lot of diseases and especially when it's a rare disease like MDS where nobody's heard of it. It's unfortunately since many people with MDS are very old and they're not the most vocal political, you don't hear about the disease very much until a celebrity like Nora F. Ryan or another celebrity like Robin Roberts gets a disease and then you sort of hear about it as a blip and then that's about it. So, it's not a commonly talked about disease.

The old name for it was preleukemia which was abandoned more than 10 years ago because fortunately it doesn't evolve leukemia in most individuals and so we though that was a bad name, but myelodysplasia doesn't really have a catchy ring unfortunately. So, it's one of those diseases that sort of goes under the radar but is a fairly common disease. So, you're actually not alone. I've heard you say you haven't met anybody. It's because most people don't know it's not like there's a big advocacy that you would talk about. There's people here and there, but it's always sort of under the radar and it's usually the one person sitting in the back getting the blood transfusion and often it's an older person in the back who's weak and tired and getting a blood transfusion in the back and so it's not the forefront of Hodgkin's disease which everybody in this room I'm pretty sure has heard about. Hodgkin's has much fewer patients, very few, 3,000 to 4,000 in the United States at any one year whereas MDS maybe 10,000 to 40,000. It gives you an idea, but who gets Hodgkin's disease? The teenager who's… once the teenager in the high school gets it everybody in the town know about it, but when the 80 or 90 year old gets MDS and is sort of tucked away we don't hear about it. So, it's sort of one of those weird diseases.

So, let me just give you my take and then later on I'm going to give a more formal presentation.

Q3: Do people maybe have it for a long time before they ever realize and get diagnosed?

Dr. Stuart Goldberg: Yeah. So, MDS can be a very insidious disease. It doesn't come on all of a sudden. It's in a group of disease which we call the bone marrow failure disorders. So if you think about in your hip you're making blood and as you've heard and I'll show you some other slides down the road you've that blood has three main parts. There's the reds that give you the energy and the oxygen. So, think of them as the trucks. They carry oxygen from your lungs to your muscles. If you muscles get fed you can get up and walk. If you muscles don't get fed you feel tired and as that blood counts fall down you feel more and more tired. Now if you sit down and you're not moving, you may feel okay because your muscles don't need much, but as soon as you want to get into high gear then all of a sudden you feel more tired and the development of how those factories slow down can occur over long periods of time. So, to answer your question there are people who have myelodysplasia and may not know it for many years and actually when they come to see us and we get the blood counts from the last… can you have the family doctor send me your blood counts for the last year. We may have seen that red count in a man 14 pints or hemoglobin of 14. Think of a gram of hemoglobin is about one pint of blood. So, a normal healthy man has 14 pints of blood. A normal woman has about 12 pints of blood or a hemoglobin 12, hemoglobin of 14. We may see that that went from 14 to 13 to 12 to 11 over the

last three or four years before the doctor actually even said uh oh, now let me send them to a hematologist, a blood specialist who also may be a cancer specialist that before that is even picked up that there's a problem and many times I'll even see patients and say you may have MDS, but why should I bother sticking the needle in your hip because if I find it right now you're still functioning and I'm not even going to do anything for you for a while. So, the question of when do you start which we heard our last speaker talked about is a very, very difficult and complex question. I mean, there is not a good answer for that and they really have to look at what does the patient want to do. I have a very delightful gentleman and his wife that I've been taking care of for many years and his blood counts were failing and we talked about therapy and when you talk about giving blood transfusions and he was getting low and his wife said to him I want him to get some blood. I want him to get some blood. He just sits in the bed all day and sits in the chair and watches TV and he doesn't get up because he's too tired and then she went out of the room and as soon as she walked out of the room he turned to me and said, "Doc, don't bother with the blood transfusions. I'm happy in the chair." So, but that I think… if he was a 55 year old lawyer who I also take care of I have to keep his hemoglobin up 12 or more. Why? Because he's competing with 35 year olds who want his job and if he can't stay up till ten o'clock or eleven o'clock at night working then he's not going to be at the peak performance. So, whereas the 80 year old who's happy sitting in a chair might let me let his hemoglobin drop to 8 ½ - nine… eight or nine pints when it should be 14. The 55 year old tells me any time he gets below 11 he feels tired and can't keep his activity up to the level he needs to be functioning. So, when do I start therapy? You could see it be very different between those and when do I start to make even the diagnosis because this could have slowly spelled down over many years.

When I meet a patient with MDS, typically it's because the red count's low. Usually, it's because they're anemic. That's what the family doctor notices on the blood counts that their red count has fallen. That's often the reason why the person went to the doctor in the first place is they started feeling more tired. Occasionally, you meet them because their platelets and platelets their job is to stop you from bleeding. They're the clotting cells. Occasionally, it's because the platelets are low and a normal platelet count's 150,000 or 150 on your sheet. Anything above 100, who cares? It might be a little bit low, but you can go through an operation and you won't bleed. As it gets below 100, we start to see the risk of bleeding goes up and it really starts to occur when you hit below 50. So often even if it's above 50 as long as they're not… don't play soccer and things like that. We tell people don't do work, but once you get below then we start seeing bruising and I banged myself I got a big bruise. Once you get below 20, I got a bruise and I don't remember why and unfortunately if we get below 10 then people can start having internal bleeding and that's where it's real dangerous. So, that's where we actually will turn even to a 90 year old and say, "Look. I know you don't want chemo, but a platelet count that that's low you may bleed and you may die from this disease and we may need to do something even if you're 90 years old," and that's the discussion that we have to sometimes have. So, if the person's feeling fine and they're not… they get a blood transfusions and they feel okay. I don't know what the rest of your father-in-law's blood counts were. I mean, if he's feeling okay and his blood counts are still in the safe zone then you're talking about some question of quality, but once your numbers get so

low then you do talk about quantity of life and then that's the decision we have to say look if you do this we may change that course. So, we go from a sometimes in the beginning of this disease, a quality disease and unfortunately for some people it becomes a quantity disease, but not fortunately for everybody.

The third cell is the white cell and you heard our last speaker talk a little about ANC because the third cell is the white cell and the white cell, its job is to fight infections. So, a normal healthy person has 5,000 white cells. We call them neutrophils or myeloid cells. That's why the ANC. Of the 5,000 white cells that I have, 4,000 are the neutrophils and their job is to fight bacteria. They're the cells that keep you safe from today's infection. One thousand of them are lymphocytes and lymphocytes their job is to make antibodies so you don't get the same infection twice. So, that's what the vaccines work on. Now in MDS, it's the neutrophils that fall apart, the bacteria fighting cells and when they get low if out of my 5,000 white cells that I have, if 4,000 of the neutrophils I'm pretty good. If somebody coughs on me I'm going to do okay. As that starts to fall down and they cough on me I get more risk for infection. So, that's why if we see it above 1 ½, 1.5 or 1,500 neutrophils that's probably enough white cells to keep us away from most infections. Once we get below that all of a sudden the white cells are now we don't have the bacteria fighting cells and more and more infections. So in my patients with bad myelodysplasia they get an ear infection followed by a sinus infection followed by a urinary tract infection followed by pneumonia. I mean, every time I'm seeing them I'm writing a prescription for antibiotics. Once again, that would be one of those times when I'd twist somebody's arm and say, "Look. We can do the antibiotics over and over, but maybe we need to focus on treating the underlying disease."

So, there is a bad balance of when do you start. Some people we will start treating them just because we see the numbers before bad things have happened. Certainly, younger patients we're going to be a little more proactive. In older patients where their decisions of should I do this or shouldn't I do this often are driven by are they down into danger zones or do they have cushion and they don't want to get therapy.

So, those are some of the questions about how you start and when you start.

Why? That's always the next question I always get after I look at the blood count and say here's your blood counts. This is where you are in the spectrum of your blood. The natural question is why and for their, I often will say talk to your clergyman. They're better than answering the why questions than a doctor, but there are some medical reasons why people get this disease and this is really a disease of the environment. This is unfortunately we done to ourselves. This is chemicals, poisons things like that. Being exposed to these type of things puts you at risk for developing damage to the bone marrow. So when I talk to a lot of my patients with myelodysplasia and I ask them what did you do for a living? Oh, I worked for the gasoline/petroleum industry. In New Jersey we see a lot of that or my hobby is that am a painter and I have my thinners and all that stuff. The (inaudible 14:37) the benzenes and it's usually low

dose, low levels of a poison for a long period of time. It's not somebody oh I walked in once to a painting gallery. No, but if you did painting or you worked with photography and you develop your own prints and you do that every day for years that's the type of people who the chemicals can start damaging the bone marrow.

So, what do I mean by damaging the bone marrow then? So, we see this person comes in. They have lower blood counts. We start sticking needles in the hips. Why in the hips? Because if you think a dog bone that's what your hips look like. They're hard on the outside, hard on the inside and there's a red core in the middle. That core is called the marrow and that's where the factories are that make blood. When you were little you made it in all your bones, but as we got older and our hips got big these bones all become scarred and can't make blood there and it's basically your backside and a little bit of the breast plate called the sternum. If there some other diseases where you scar those things up called myelofibrosis which can go along sometimes with myelodysplasia where you scar that the blood factories can actually go back to the spleen which sits… I do that on this side and I know the spleen is in the upper left hand corner, upper left hand corner and that sometimes will get a little bit bigger in our myelodysplasia patients because that used to be where you made blood before you had bones when you were an embryo. So, these are where you make your blood.

So, we stick a needle in your hip and what we see is an ugly looking bone marrow. Dysplasia means change. That's where the name comes from. Myelo is blood. Dysplasia is change. So, what you're actually seeing is the factories themselves that make the blood are broken and that's the disease. If I have a person who comes in with low blood counts and I stick a needle in her hip and the bone marrow looks completely normal and completely making… the factories look all normal this is not myelodysplasia. So, by definition you have to see the ugly looking factories and there's a whole bunch, John Bennet, who helped start this organization is a pathologist. He looks on the microscope and he comes up with some other names when we get confused the bone marrow looks good, yet the blood counts are bad and we can't find some other vitamin problem. So often probably many of you when you're first diagnosed the first thing the doctor did was they did an iron level and a B12 level and a folic acid level and maybe copper and zinc because these are the vitamins you need to make blood and worldwide the most common reason I have low blood counts is iron deficiency. So, but that's not what the problem here is. The problem is then did you have a vitamin problem. Your problem is that the factories even if you gave the baker every little component the factories to put it together are still broken.

So, that's the disease. The disease has to be made by the pathologist telling us that the factories are broken leading to you have low blood counts. Which counts are low depends on we'll then determine how you're going to feel, what's going to happen to you and there are people will just have low red counts and be tired. There are people who have low white counts and being infected. There are people who have low platelet counts and they'll be bleeding and there are some people who get, unfortunately, two factories broken or all three factories broken. Most

commonly it's just the red, but there are people that have all three and there are people who just have one depending on which factory is broken.

So far catching and okay?

The next question is low grade and high grade. You heard that a little bit on the last speaker. So after somebody says okay, doc, you have me a name of what I got and there are fancy names for it. Myelodysplasia is the grab bag name and then the pathologist will look and say, "Well, the white cell factory looks ugly, but the red cell factory doesn't," and that's one name and so there'll be 10 or 15 different names we now have them as five or six that are codified all the time. So if you what's called the pathology report, and I agree completely with the last speaker, always ask no matter where you are you always want to get a copy of your path report. Put it in your file because somebody's going to say down the road, grandchildren are going to say, "Didn't grandma have something?" and you're going to say, "Yeah. It was this kind of this disease and it was this type of subtype." Pathology report just what they saw on the microscope. Nice to have in your file. You may never look at it again, but just have that and every doctor will be able to print that up for you. So, I actually hand it out with every consult. Just one of those things that you want to just have that piece of paper. So that way you can look on the web and say okay this is what I have, this is the kind.

But after the pathologist looks at it and gives it a name the next question is the patients usually ask me is so what does this mean and really what they're asking is am I going to live or die. Can you give me some idea on prognosis? Where's this headed if I decide to do nothing? Because you want to know. And that's a question that, frankly, any doctor worth their salt should be willing to answer. So, don't be afraid to ask your doctor how am I doing, am I on track and what happens if I stop and what happens if I get treatment because these are questions that you deserve the right and you deserve a straightforward answer. If you don't get a straightforward answer tell the doc look, I want a straight and forward answer. I need to know. Now, you may not want that. Not everybody has to run out to the doctor and ask that question. That's a decision if you want to ask that question the doctor should give you the answer. If you don't want to know that's allowed, too, and we shouldn't as doctors force ourselves of what we think onto you.

You should tell us what do you want to know, but very typically people at least want to know an idea of what's going on, where am I especially when I'm first diagnosed and so we use a couple different terms. Low grade and high grade is a nice split. So, think of it what is the disease? There's low grade and high grade. The best way I think of myelodysplasia to describe it to somebody who doesn't know the disease if you're going to have to tell somebody else what do you got. It's our bone marrow factories are dying and they're not producing blood anymore. So, think about a garden. You got a garden it's so big. That big. Okay? And in there you have factories. You have red plants and white plants and platelet plants that are making red cells, white cells and platelets and these factories are producing blood, producing the different types of blood and giving you all the energy and all the clotting ability and all the infection fighting

ability that you need and then something damages one of those plants or damages two of them or damages all three and gradually what happens is those plants start to shut down and as they shut down they produce less blood. They produce less fruit. So now, the red count starts to drift down. That's low grade myelodysplasia where the factories are basically shutting down and they shut down at this speed and that speed is usually measured in years. So, they will slow down and that's why people can be diagnosed for many years and really not much happens, but slowly if it gets low enough it can bring people to somebody's doctor's attention and it can go so low that it can actually cause people to die. I mean if your platelet gets so low that you trip and fall and you bleed that can be very dangerous. So, just because it's low grade doesn't mean that it's not important especially… but we really typically think of low grade more as a quality issue because you're tired, you're more easily to bruise, you're getting more infections until it gets really, really low but then it still can stay low grade and in 80 percent of the people that's how the disease goes. It just continues to fade away over time and over years to the point that unfortunately people do start to die from infections and bleeding.

Now, in about 20 percent of people the disease changes to a high grade disease and it may have actually even presented earlier like that. What's high grade disease? Well, you got your plants that are disintegrating slowly and then all of a sudden a weed comes along. What's a weed do in a garden? A weed takes up energy, it takes up space, it takes all of the nutrients and it even kills the plants and the weed is what's called a blast. A blast is a leukemia cell. It's a factory that's so broken that all it does is take up space and energy. Now, most people never have that. Most people it just fades the disease the bone marrow just sort of shuts down, but if those weeds come in there well then we worry about it and so when we start seeing weeds that's when we start using the word 'higher grade.' If you have a few weeds, five percent or less then what does that do to your garden? Probably not much. So a low grade disease, many of us will call low grade, if you have five percent or less leukemia weeds, five percent or less blasts because for the most part how the energy is going to be and how the bleeding is going to be it's going to be dominated by how the other plants are doing, but once you start to get more than five percent weeds in a garden then all of a sudden they were taking nutrients. So somebody whose blood counts were slowly going down all of a sudden fell like they're going off a cliff because now it's not just the factories disintegrating it's also the weeds starting to kill the other factories and when does the whole factory fall apart? Over 20 percent. That's what leukemia is. The disease, leukemia, if I see a person with leukemia they've got all weeds and no plants and so therefore they're not… without plants what's happening? They don't make blood. Their red counts fall to nothing, they need a blood transfusion every day. Their platelets fall to nothing, they're starting to bleed unless I give them a transfusion of platelets. Their white cells are so bad they're getting infections.

Now, so it's a dynamic between dying plants and emerging weeds and which plant is broken, how many plants are broken and how many weeds and how fast the weeds decide to grow is what makes each of you different than the next one because there's not one size fits all here. There are some people that like you who have a broken red factory with specific gene that's going to tell that gene… that factor to die at a certain speed. It's actually going to tell your

platelet factories to overproduce and so probably if you look at your original platelet counts you probably had higher platelets than average because it over produce so you weren't at risk of bleeding and there are other people in the room that probably had low platelets when they started. So each person's different based on which factories are broken, how many weeds and what happens and it changes over time depending on which chemical, which poison, which genes decide to break in those factories.

That's the underlying disease.

Now, to get more technical in it and to help the doctors really give you an idea and help us plan for our therapy we developed something called the International Prognostic Scoring System or IPSS and now we've revised it called the RIPSS and these are mathematical formulas by looking at thousands of patients and saying, "Okay. I have had 1,000 patients in my career and these 800 did well and these 200 didn't do well and what was different about these people than that?" So, we've gone backwards and said if you had these that was a bad thing. If they had this… So, the IPSS very simple. The simple version of it before we get into the mathematical ones and these are the type of things that make sense. One, if you have just your red factory broken, you're tired, but you're probably going to live a lot longer than if you have tired and you're bleeding and if you're tired, bleeding and infected that's probably not as good. So, the more factories that are broken the more trouble you're possibly can get into the worse your outcome. So when we're developing the IPSS, we said, "Look, how many factories are broken and the more factories are broken the more worried we are about the patient," and that gets you points on the IPSS. Second, how many weeds you got? If you only have a few weeds, well the garden is going to do better for a longer period of time. The more weeds you got the more likely the whole factory is going to shut down, the more trouble somebody's going to get. So, the second component of the IPSS is how many blasts. So, how many factories are broken? How many blasts? And then the third really is the more scientific one and that is genetics. We can now go into those bone marrow and look at the inside of the factory. Yeah, they're ugly on the outside, but what do they look like on the inside of the cell. The cell's broken at the genetic level in the middle, well that's going to give us a clue as to how fast it may disintegrate. Some genes when they're broken so example chromosome five, that one tells the red factory tells the red factory to break and slow down at a very slow rate and so actually people with 5Q breaks tend to live a lot longer and we actually will move them as not as worried. On the other hand chromosome seven is another chromosome that's frequently seen in MDS. When that one breaks, that one tells us that the whole factory is going to disintegrate over a course of one or two years. So, we can see a disease where five is broken we think of bone marrow disintegrating over five or 10 years. Where chromosome seven is broken we see a bone marrow that's going to disintegrate over one or two years. So, we can use this information how many broken factories, how many leukemia cells and where the genetics to build a picture of is this person somebody we should be very worried about, moderately worried about or not too worried about at all and so the IPSS gives the doctors and the patients some guess of where they're going to be and that's the purpose of it.

So, the formulas are going to be in the app. You can look them up. I'm sure your doctor has calculated them. You can calculate them and the question is can you recalculate them so when somebody has a bone marrow every other year or something like that do we recalculate? Yeah. We can use that and recalculate and say okay this is where they currently are.

Now, the scary part about the IPSS they actually talk about survival, how many years people live with that disease once they have these things happen. One important thing to know about the IPSS though is that is natural history. In other words, no treatment. We designed the scoring system to say what happens if we diagnose somebody and then they step away. Now, by no treatment I don't mean no treatment at all. We would give them blood transfusions and some basic antibiotics, but if we don't intervene with any pills or chemo or IVs or things like that and we just let the disease progress at the speed it's going to progress at what could we expect? So, that's how they develop the IPSS because that gives us an idea of where this person is. Hopefully with intervening we change that curve, we change that course, but the scoring system was developed to be what would happen if we don't do anything about it.

So, that gives you an idea of what the disease is why it's important because it's important because how many blood factories are going to give you different symptoms and how we prognosed it.

Questions about any of that so far?

How do we treat it and then I'm going to talk about something different after the break. So, a question of treatment becomes what do you want to accomplish and so this is actually one of those rare diseases when I have a patient with MDS. When I have an acute leukemia patient I'm actually a bone marrow transplant doctor, too. That's what my original training was in. What do you want to accomplish and that's not an easy question. Are you trying to cure somebody so that they can have another 40 years like Robin Roberts? She's young. She's got this disease. She had high risk disease by the way. She had a monosomy 7. I actually know her because I know her doctor. She's from New York, by the way, my hometown. So, does somebody have a very bad ugly disease, IPSS high grade or high risk where if we don't do anything they're going to decline very quickly. Well, then we might want to intervene with something a little more aggressive. If somebody has a very low grade disease, a 5Q- where they're not having much symptoms, the counts really not bad and we say, "Look, even if we don't do anything they're going to coast for many years. Well, we maybe aren't as aggressive," and so we have to put in how old are they, what do they want to accomplish in their lives, how close are they to diabetes and heart attacks and all that other stuff happening that maybe we're not the most important doctor. Maybe it's their heart doctor is the most important. So, you have to balance the whole thing and then what do they want to do? Is he happy sitting in the chair or does he have to run up the stairs to compete with the other lawyers? So, the decision of what you do depends on what you want you want to accomplish. So, you have to talk to your doctors and nurses and say what do I want out

of life? Depending on what you want out of life and where you are in your life it may be very different.

For many people in the beginning of the disease when it's lower grade, when it hasn't advanced very much and mostly it's anemia, tiredness, it's a matter of giving them blood transfusions and getting the energy back up and then when the energy is back up how do we keep it up and so the most common therapies in the United States are blood transfusions and then some type of fertilizer, growth factor. The growth factors we typically use are some drugs called Procrit or Aranesp. What are they? They're actually chemicals that are made naturally by our kidneys. It's our kidneys' job to tell us to make blood by the way. If I cut myself and bleed a pint on the floor, how does my body know that I'm down a pint, well the kidneys know that I'm processing 14 pints of blood every hour and if all a sudden Dr. Goldberg bled a pint on the floor the kidneys will say hey, I'm under working. It'll send a signal to the bone marrow and make more blood. So, when I was a fellow back in the… this is probably in the '80s, they actually had discovered that this chemical called EPO was made by the kidneys and if you bottled it up and genetically engineered it and gave people a shot of EPO you basically are putting fertilizer down that tells the body to make more reds.

So, how do you fix a plant that's dying? Well, maybe you squeeze a little bit more blood out of it by giving it a little more fertilizer. Does it fix the plant? No, but does it squeeze a little more drops of blood out of it? Yeah. You can get a dying plant to give you a little more fruit by putting some more fertilizer down. There are two of them on the market, Procrit and Aranesp, and as you heard the MDS Foundation helped keep those drugs on the market. There were some problems that if you give those medications to people with breast cancer or colon cancer yeah, you make them feel better while they're getting the treatment, but it also makes the cancer… they're a fertilizer. So, it makes those cancers get worse. And there were some economic problems the feds actually… but the bottom line is that those are there. There are experimental Procrit type drugs that are coming out. We may actually have a new one next year. So, there are other ones in that type of family. There's also drug Neupogen or Neulasta or Leukine. These are fertilizers for whites. So if somebody has a very low white count you can actually give the fertilizer and get the white cells. Now, the MDS Foundation actually does have in their booklets that they don't recommend on a routine basis to give those every day or every because they're very short acting, the white ones. The red ones very common to use. We fought for it and we give that and try to keep the blood counts up and prevent you from needing transfusions, but the white ones they work and then two days later they're stopped. So, typically we tend to reserve those for persons who are in the hospital with an infection because they're very expensive and using them chronically gets the white count up, but you probably do that better with just getting an antibiotic here and there. So, there's other ways to get around it, but some doctors will use intermittently the white cell fertilizer just to keep people tweaked. There's a little style. There's a lot of disagreement in the field. If your doctors doing I'm not going to fight. There are things that are disagreements in the field and there's probably some literature supporting my view, but I'm always right.

Unfortunately, we don't have great fertilizers for platelets. There have been a couple that have been out there. There are drugs that are being used to help platelets go up. They've had some starts and stops in the MDS world. We do have them actually for other diseases. In MDS it's been a little bit more tricky. Especially in Houston they are big advocates of one of them for a certain and they actually done some research in one of the drugs to help platelets during chemotherapy and I actually participated in those trials, but that's one where I will tell you that we don't have a pat answer, but the fertilizer for red pretty much out there for all the time. The fertilizers for whites intermittently if you need them because you're sick with infections and that's usually where we start.

Now as the disease progresses and more and more blood transfusions occur, we get into problems with the complications of transfusions which I'm going to talk about next. That why I was actually was invited to talk about, but we were ahead of schedule so they yanked me to talk a little more. Then at a certain point though all the fertilizers in the world aren't going to save a dying plant. So at a certain point you may want to actually try to work on the plant itself and that's where we talk about chemotherapy and yes, I am a cancer doctor in addition to being a blood doctor. Chemotherapies though can come in all shapes and forms and the chemos that we're going to use to treat myelodysplasia are not there designed to kill the cells. They're there designed to make them to work better and there are three FDA approved drugs – Lenalidomide also known as Revlimid. It's a knock off an old medicine called Thalidomide. Remember Thalidomide from the 1950s where the babies were born without arms, but it turned out that the blood counts actually ran up in the women who were pregnant and they actually noticed that and years later they came up with a whole set of ways to use Lenalidomide or Revlimid. The reason you have to fill out tons of paperwork and tons of paperwork every month because the child advocacy groups you figure never wanted that drug to see the light of day. So in agreement with the FDA they said, "Look. We know this drug is horrible when it comes to causing birth defects, but if we make sure that it never gets in the hands of a pregnant woman then it may have its benefits." So, that's why there's tons of paperwork and believe me the tons of paperwork you're doing now are nothing what you had like when I'm do a spec in the '80s. We had a patient actually… one of my patients actually snuck it in from Germany, Thalidomide, because to treat his disease before it was available in the United States. So, that's what Lenalidomide is today a pill that basically tells the red factories to start growing. It doesn't do too much for the whites or the platelets. It may have some effect, but when they did the original testing they found it didn't work on everybody with MDS, but if somebody had a chromosome five break it could be dramatic. Two out of every three people who took that medicine all of a sudden blood counts would get better and the blood counts would stay better for a long period of time. If you didn't have chromosome it could make it go up but not as frequently and so the FDA said you know what, that's really not the indication. It doesn't mean the doctor off label can't use it and certainly I've written many, many times off label for Lenalidomide or Revlimid to treat patients who have low red counts and there are randomized clinical trials. A big one that's going to be presented in a couple weeks at the ASCO meetings trying to get that drug on the market for those

patients also so the doctor doesn't have to do it. I know because I'm the coauthor. So, that's an international study to get this drug mostly in Europe because the Europeans can get it, but Lenalidomide helps the reds go up. It doesn't do much for the whites and platelets, but it's often a first step for somebody who just has low reds.

The other two drugs that are on the market are Vidaza and Dacogen are the brand names or Azacitidine and Decitabine and these are weird type of chemos. They're given one week per month and how long is a week depends on where you live. In New Jersey I don't like to work on weekends. It's five days a month. In Cleveland, the Cleveland Clinic, they like to work on Saturdays, but they don't work on Sundays. So, a lot of theirs are six days a weeks and if you go across the street into New York City at Cornell they believe in seven days a week. So, because they have fellows who work on the weekends. Not that big attendants don't come in, but figure it's one… and so there's arguments you can see, but one week a month and what these drugs do they're given either through an IV or given as a shot. These are weird kind of chemotherapies because they can stimulate a plant and kill a weed. They do both. Actually the mechanism is actually starting to be understood in that they glop on to the genes and if a little bit glops on they stimulate the cell, but if a lot glops on they kill the cell and blasts have a lot of genetic problems. So, therefore a lot of that glops onto the blast the blast gets killed. So, it kills the weed while it stimulate the plant.

So in a person with a higher grade disease, where the weeds are starting to take over these are a type of medications that can kill off those weeds and stimulate the plants and so in a classic study called AZA001 which is actually described in the MDS book that you probably have that they were giving out this was a big international randomized trial where half the people got just transfusions and half the people were given one week a month Vidaza or 5-Azacitidine. For people who had higher grade myelodysplasia because you're not going to give it to somebody who just has low red counts and no blasts, but if they have multiple blood counts that are broken starting to bleed and bruise if they have lots of leukemia cells where we say uh-oh the weeds may take over the garden half the people got the Vidaza, half the people got the blood transfusions. The bottom line is more people were living who got the Vidaza than who got the blood transfusions. It stimulated the blood. It kept the leukemia cells from taking over and it improved survival and what was the cost? Well, guess what? When they ask quality of life questions the people who got the chemo said that they felt better than the people who got the blood transfusions. So for you with your 90 year old this may be the type of questions that you need to ask the doctor. Now, there are other things that are going on. You got to ask, but people think of chemo and they say they got worse. Well, having low blood counts and being tired all the time doesn't make you feel so good and if you can get those plants to start functioning the energy level can go up and the bleeding can disappear and the infections go away and then in the long run the quality may actually get better. So, there may be a little dip and if you saw that slide there the first two or three months when you come in with a weed killer what's going to happen? You're going to have an empty field. So, the blood counts get worse the first two or three months and people do feel worse the first two or three months, but then the healthy plants start to come

back in and the energy level gets better. So when I had somebody who's on the edge, I tell them, "Look. If you're willing to suffer…" not really suffer suffer, "but if you're willing to put through a couple months of feeling a little bit worse in the long run you're going to feel better." Now, some people say, "Look. I don't want to feel worse and I don't need that extra energy and my blood counts aren't that bad and I don't have that many leukemia cells then maybe I don't want to do that." So, there are people that I say on the scorecard you look like you should get it and when we talk to them they say maybe this isn't the right thing and the other thing on that slide was it takes four to six months for these things to kick in. So, the biggest error and biggest disappointment I see when I do second and third opinions is when somebody's gotten one cycle they feel lousy and they stop and they often will like a month or two later come to see me for a second opinion. I say, "Look. You started and you got all the downside and didn't stay with it long enough to get the up side." So once you commit to this you have to commit for at least four to six months and my friend from Cleveland Clinic who's one of the world's experts in MDS his comment was when patients ask how am I doing, he sticks his head in the sand and says I won't answer your question until six months from now and at six months now I'll give you an answer because I can make them feel worse the first couple months as I'm trying to make you feel better and in the long run we know in the randomized trials where half people got it, the people did say it was worth it and we're talking about 75, 85, 90 year old people, but that doesn't mean it's right for everybody.

And finally and I'll stop because I don't aware of my time is there a cure for this disease and what do we do for the young, young person who doesn't have the weird 5Q? You're in the minority by the way which is good. You're in a good minority, but what do we do for the younger person who says, "Look, I want to be cured?" And younger is technical. We've done into the 80s by the way for bone marrow transplants at our center. When I started anything over 45 was old. My first transplants back in the '80s, we wouldn't touch anybody really over 40 and now we're thinking routinely up into the 80s if they're an 80 who walks and talks and feels energy and can do things and has to have a good heart and good lungs and good things like that and so monitoring blood counts and looking at kidneys and liver and all that stuff important to do probably with these drugs. Any of these drugs every couple months at least. So, I agree with you. You got to tweak your doctor and make sure that they're following just not the blood that they follow another which I'm sure they do. That's pretty common. Often you can't tell with our orders we said, but we can cure this disease, but the cure comes with a lot of price and that is a bone marrow transplant.

Ten seconds of what a bone marrow transplant is by a guy who actually does them. So, that's always… I hear family doctors tell the family, oh, you don't want this because… or cancer doctors who will give all kinds of crazy numbers because they don't do it. I do it. I've been doing them for 30 years. What we do in a bone marrow transplant in myelodysplasia today is very different than what I did when I wasn't going to treat anybody the age of 40. Most people now get what's called a mini transplant. That's a misnomer. Mini means mini to me compared to what I used to do not what the patients feel. A mini transplant is a month in the hospital and a

year of their life. If I say that then that's enough to really at that point. What happens though in that first week is we give them poison and now I am talking about chemotherapy. If you want to fix the field and you got broken plants, you got to burn them down. So, people come in the hospital in that first week we destroy the whole bone marrow, good, bad, anything, wipe it down to that garden that has no plant left. Now, what do I mean by mini? We've learned that we don't have to hit them as hard to get wipe it down. That's the difference. So, we've given less chemotherapy but at the end of the week that bone marrow is pretty much dead. We then turn to a donor, a brother or sister, an unrelated person who happens to have the same bone marrow type that you called HLA typing. Now, we can actually do even do half children, with children who are only going to be half of you. Much more risky, but we can do that routinely. Twin by the way, no good. Throw away your twin. Be nice to her, but…

Q4: (inaudible 49:53) say no and another doctor says yes.

Dr. Stuart Goldberg: Absolutely no. Not even a question. If it's an identical twin. Identical twin will not work. Eighty percent – 90 percent relapse rate. Not even worth doing it. So, I mean… so get rid of that. I'll explain.

So what we do is destroy the bone marrow, turn to our donor, take out blood from them and when I said blood that's called a stem cell transplant or we can take out bone marrow from their hip. That's called a bone marrow transplant. So, the only difference because… I talk about… I go through a whole consult with a person and tell you all about bone marrow transplant. So, what about this thing called a stem cell transplant? Well, the difference between a bone marrow transplant and a stem cell transplant is what do with the donor. Do I take it from their blood or do I take it from their hips? For you it's the same thing. It's the same deal. Take those seeds out, put them into the arm, they float around, they land in the hip. It's like throwing seeds in the air. When they hit the ground they start growing. Counts are up here. I give chemo therapy. They go to nothing. I squirt in seeds, wait, wait, wait. A month later they grow back. That's why you're in the hospital for a month. During the old bone marrow is dead and the new one hasn't grown back you're a sitting duck. So, you're sitting in the hospital with blood transfusions every day, antibiotics every day. Watch for infections, stay in a little bubble, a lot of care to keep you alive essentially. Believe it or not we're actually pretty good at doing that. Get most people through the transplant. The danger of the transplant is when the counts come up and everybody's happy because when those seeds grow back they're not you. You know have somebody else living in your hip. So, rejection. So over the next year, you're seeing the doctors every single week, sometimes every month if you're really doing well till we get that new bone marrow to like living in his new hip. So somebody asked do I have to be on medicines if I changed to a transplant, the answer is yes. You're not on medicines anymore for MDS. You're on medicines to keep that bone marrow happy because that bone marrow doesn't want to live in you. My white cells, my immune system is there to keep me free from infection. Somebody calls to me that germ looks different than me. Different things don't like me and I don't like different things in my body. My immune system will kill it. If I put your white cells in my body, now your white

cells are floating around they will see my body as different and they will attack my body. That's called graph versus host. So, it's the new immune system attacking the whole body and so we got to keep that bone marrow happy in there. Now, fortunately in many people that bone marrow will learn about its new home and once it learns it's now its new home we can then get rid of the medicines. So, about 70 percent of the people at the end of a year are off rejection medicines because now the bone marrow has learned but there are a significant number of people that takes two or three or four years or may never be happy in there and in MDS unfortunately about one-third of patients will die during that first year from a transplant. It's a pretty high number. Now, most people with MDS are over the age of 65 and so we are talking about older patients having bone marrow transplants, but the national numbers right now about a third of patients. We will cure about a third of patients, about a third of patients will die from the MDS. We didn't get rid of every last plant and they came back and about a third of patients will die from transplants. So, one-third. For a patient who's in their 60s, early 70s who has a bad type of MDS it may be worth it. If I have a person who's walking in here. Now they have a lot of blasts, they're bleeding all the time, they're in the clinic all day getting blood transfusions and as soon as I'm done they're back here the next day and you say look, this is not a life. They may say a one-third of their dying is worth it. For a person who has normal blood counts and maybe on a little Revlimid and doing fine that kind of risk is probably not there. So, when's the right time to move to transplant? It depends on how bad the disease is. It's not the last resort. I have seen many consults in my lifetime that the first treatment was a bone marrow transplant. For Robin Roberts, the first treatment was a transplant not because she was young. She had bad MDS. She had breast cancer years before. The poisons from the breast cancer poisoned her bone marrow. She had leukemia blasts. If they didn't burn that marrow down she was going to get in trouble real fast. So, they put her on Vidaza or… actually she got Dacogen. She's been open on this. So, she got a couple months of that five day… one week a month to get things under control and basically to give long enough to get the donor ready and then came in and did the whole thing. For her the risk was worth it because if she didn't do this her bone marrow was going to fail very quickly. I could have another young person who's doing wonderfully on a drug or the blood counts aren't that bad. It may not be the time to do it. So, when is a transplant appropriate? It's when the risk of the transplant is less than the risk of the disease. For most people that's at Intermediate 2. So, there have been some studies looking at if you had somebody's brand new with the IPSS low risk, well the disease is not so bad. The transplant's dangerous. IPSS high the disease is probably out of control and the transplant may not work. So, if we have Intermediate 1, it's at low, Intermediate 1, Intermediate 2 and high. Intermediate 2 seems to be the break point, but that's on populations. Then again you have to talk to the person, how a good a donor they have, how healthy they are, where does the risk fall. That's not an easy discussion. That's one that somebody who knows transplant. So one of the few recommendations I will give you is anybody who is young don't listen to your cancer doctor on whether it's time to have a transplant or not. Talk to the transplanter and tell them and ask when's the right time? Because oncologists even oncologists in my area who've been working with me for years don't know the right timing. So, you need to have your oncologist who's taking care of you and then the transplanter who actually says this is what I do for a living. I'll tell you if this is the right time for you because the oncologist may

have not understand what's happened in the field. So, this is where you do need two doctors who will talk to each other and so obviously with young and doing well, you want to every once in a while check in with a transplant doc and say, "Hey, anything new? Where am I? This is where I am," and they'll probably say no, but that's okay, but it's worth it because you don't want to miss the opportunity when the time is right.

To why not a twin because the reason the transplant actually works is when you put the new seeds in they actually… not only do they fight the skin and the rest of your body they also fight the weeds. So, they will actually kill off… you have two plants in there now. You have your old cancerous ones and you got the brand new seeds and those new seeds will say look, I want to take over the field and the fact that they actually will fight to take over the field is what actually cures the patients. It's not the poisons I gave up front. It's the new bone marrow. Twin, their cells will perfectly happy in there right next to the cancer cell and the cancer cell will come back. So, the relapse rate, yes, it's much safer you don't get graph versus host disease, but you also relapse. So for certain diseases we don't do twins. Myelodysplasia is one of them, acute leukemia one, chronic myelo leukemia is one. For lymphoma a great disease to do a twin. So, it's not that we never use twins, but there are certain diseases where you need that fighting and that was why we wouldn't pick a twin.

Q5: (inaudible 58:15)

Dr. Stuart Goldberg: Of developing MDS?

Q5: Yes.

Dr. Stuart Goldberg: It's mostly environmental. It's mostly environmental. So, it's probably a little bit higher than the background, but it's probably… now in concordant studies there is higher but that's because they probably lived in the same place and therefore exposed to same chemicals.

Q5: (inaudible)

Dr. Stuart Goldberg: No, the deletion 5 happened after. You weren't born with deletion 5. Questions about the disease and then Im going let somebody else after somebody else.

Q6: Since she started the Revlimid her white count has dropped drastically and her neutrophils… is that just the Revlimid?

Dr. Stuart Goldberg: Yeah. So, the Revlimid itself will actually push down the white cells and it will push down a little bit on the platelets.

Q6: Platelets but her…

Dr. Stuart Goldberg: And so then we often will back off on the dose because that's more of a problem the drug. However and here's the however and I don't want to scare you, the scary part, is that could also be the underlying disease. So if we see that every once in a while, we actually will do a marrow just to make sure it is the drug and not the disease, but for most people it is the drug and then it's just a matter of lessening the dose or going to every other day. So, you play with the dose to try to find that happy balance, but that is a side effect of the drug.

I'll be back in a few seconds. There's some legal things I have to say goodbye.

Audrey Hassan: Thank you, Dr. Goldberg. We're going to take a five minute break if you want to do a bathroom break, get some more refreshments, coffee, water, anything and we'll rejoin back in five minutes.