

**Susan Hogan:** Good morning, everybody. Thank you for joining us today at our MDS Foundation Tampa Patient Forum. My name is Susan Hogan. I'm Operating Director of the MDS Foundation and I know you met Debra Murray. You probably spoken to her on the phone, our patient coordinator, and she helped put this day together.

In case you're not too familiar with the Foundation, our office is located in Yardville, New Jersey, but our reach is worldwide. For over 22 years, we have been dedicated to the Myelodysplastic Syndromes and we are works are we support patients with events like this and we offer educational programs to caretakers and healthcare professionals.

So, we have a full agenda in store today and I'd like to thank Dr. Eric Padron and Sarah Tinsley, our nurse practitioner, both MDS experts from Moffitt Cancer Center for agreeing to present today and a couple things that are in addition today. We have our regular agenda, but Monday, this coming Monday is Rare Disease Day worldwide. So, what we'd like to do to acknowledge that is right before we break for lunch, if you'd like to, we'd like to have a photo with... we're going to hand out these flyers and if you could just all hold them up. We're going to post it on the Foundation's Facebook and website and put it in the newsletter just so we acknowledge the Rare Disease Day and we're a part of it and then also following our event today right in this room we have a little iron overload presentation that Dr. Eric Padron is also going to facilitate. It's called "Know the Risk: Excess Iron in Lower Risk MDS." You're welcome to stay for that right at the end of our program. Just stay in your seats and I'm not sure, I think it'll last about 45 minutes or so, but in any case I hope you find the program helpful today and a very warm welcome. I'd also like to thank our sponsors Baxalta, Novartis and Celgene. They make our day possible. So, thank you again and I'll turn the program over to Dr. Padron.

(Applause)

**Dr. Eric Padron:** I'm going to turn this on. I just had a list of questions. That's all. So, I'm okay. I don't have slides.

Good morning, everybody. How are you? So, this is my first time doing one of these patient centered talks and I had some slides presented and then about two or three days ago I got a list from Sue and the gang at the MDS Foundation of what were really excellent questions and we have an hour, from 10:00 to 11:00. So I thought and if you guys agree because really I sort of want to do whatever I can to help answer your questions in the best way I can. So, I thought maybe we can just go through any questions and detail and maybe a brief over view of Myelodysplastic Syndrome is and then just start taking questions. If no one wants to get up to the mic, I just pulled up on my laptop a list of questions that you guys submitted. Does that sound okay? Okay. Great.

So, just by a show of hands, how many people in the room have Myelodysplastic Syndrome? And how many are family members of patients who have Myelodysplastic Syndrome? About

half and half it looks like. Great. So and how many of you guys are treated at Moffitt Cancer Center?

So why don't I start off by giving you just sort of two or three lines of what I tell my patients when they come to see me and they're first diagnosed with Myelodysplastic Syndrome. What it is, what you should expect, what we sort of know about the risk factors that predispose some patients to Myelodysplastic Syndrome and then we'll open it up for questions.

So, Myelodysplastic Syndrome is a disease of the bone marrow and I'm sure especially those that have MDS here, you know the bone marrow is the factory where we make all of our blood through a process called hematopoiesis and in that bone marrow of patients with MDS, there's sort of a unique problem. So, if I take a bone marrow biopsy slide and look at a patient with MDS, say a 70 year old patient, we should expect to see about 30 percent of the bone marrow consist of cells, the cells that are responsible for making blood and about 70 percent fat. If we take a patient with MDS around that same age, it's actually flipped around. In fact, many times more. So patients with MDS have a bone marrow that's chock full of cells, chock full of these progenitors that are destined to turn into the blood that you need, but as all of you know the main problem with MDS is that we have low blood counts. So, why is that irony where the factory is sort of chock full of these cells that are supposed to turn into blood, but yet you don't have any blood and really there are two reasons for that. So, the first reason is that patients with MDS have a defect in the maturation process of their blood. So, those cells that are there are immature and so they can't turn into the blood that they need to, but they're still present and second they die. So, the cells that are there die earlier than they should through a process called pyroptosis that Dr. List lab here at Moffitt is pioneering and understanding and what we also know about sort of that underlying biology is that in the vast majority of people, in fact, almost everybody with MDS we can find that there are genetic changes that are either directly responsible or highly associated with MDS.

So what does that mean? So, what I tell my patients is that it means that 1) you didn't get this from your mother and father and you can't pass it onto your kids in 99.9 percent of cases. What I mean by genetic changes are things that happen and are acquired through all of our lives, but that you weren't born with and that they're acquired for a variety of reasons not the least of which is that the machinery we have in our cells to replicate DNA is very, very accurate but not perfect and so as you can imagine as we get older the number of times that these this machinery can have a chance to make a mistake goes up and so stochastically sometimes even by chance we think that some of these genetic changes occur, but there are also environmental things that can predispose for these genetic changes to occur. So, some of them that have been associated with MDS are, for instance, organic solvents like Benzene. There're epidemiologic studies that say patients that are sort of intimately exposed to Benzene for decades have a higher incidence of Myelodysplastic Syndrome. One of the more common reasons are patients who have another cancer, receive chemotherapy or a high, high doses of radiation and then subsequently develop Myelodysplastic Syndrome in part as a result of the fact that they had chemotherapy. That

happens in about one percent of all patients who get chemotherapy for their cancers and then some rare reasons are sort of if you were in Japan when the tsunami hit and the reactor blew, gamma radiation has also been associated with the development of Myelodysplastic Syndrome, but really the number one thing that's been associated with Myelodysplastic Syndrome is getting older.

So, this is a disease that is age related. We know the incidence dramatically increases with age. We know the average age of someone with MDS is about 70 years old and we know actually within the last 12 months that there's actually people walking around that have those genetic changes, but have no problems in their blood and we know that the incidence of people who have those genetic changes sort of benignly walking around also dramatically increases with age so much so that if you're over the age of 70 years old you have a 10 percent chance of having these genetic changes which is in stark contrast to the rarity of Myelodysplastic Syndrome. So, you can imagine a model where we think that people as they get older acquire these genetic changes as either a function of age or their environmental exposure and then ultimately some of these people go on to develop Myelodysplastic Syndromes for reasons we're not sure about yet, but we're working hard to identify and so what's sort of very briefly kind of what we know about MDS why some people get it.

What do people with MDS experience? What should you expect? So really, I say two things, 1) is low blood counts. What you hear doctor calling cytopenias and so what? You have low numbers. Well, what you'd experience is a direct manifestation of your low numbers. So for instance if your hemoglobin is low, say, lower than 9, 8, 7, most people feel shortness of breath. What we call dyspnea exertion. You walk a certain distance that usually you're fine doing, but you all of a sudden are exhausted and tired and some people can even get chest pain, headache because, frankly, they just don't have enough red cells to carry oxygen to their organs, but if you give them a blood transfusion they feel better. The same thing with low platelet counts. You have a threshold usually 10,000 or below where patients can start having very easy bruising, nose bleeds and sometimes serious bleeding events, but again if you transfuse them the risk of having those events goes down.

So, why shouldn't we transfuse you forever? Well we know that 1) you guys know better than I do it's a pain in the butt. You have to be in here for four hours at a time, and 2) there are problems with getting especially red blood cells and we'll talk about that at 2:30, but also your body can attack those cells after a while they can make antibodies against them. So, in patients who need transfusions treatment is really important. The second thing that people have to worry about is in about 30 percent of everybody with MDS they go on to transform to acute myeloid leukemia which, of course, is a much more aggressive disease that requires much more aggressive chemotherapy. Now, I'll say that acute myeloid leukemia and MDS are not an on and off switch. It isn't like yesterday you had MDS and today you have AML. Like anything else in biology, it's a spectrum and so there MDSs that behave more like AML and there are MDSs that behave more benignly and in fact there's some patients with MDS that never need any treatment

and die of something else, but there's some MDSs that are highly aggressive and we can talk about it a question and answer period how we decide or at least make our best guess as to which of those MDSs you or your family may have.

The last thing is what do we do about it? Well, if you have that MDS that is sort of the low risk, benign MDS that really isn't causing you any trouble, we do nothing but watch it. It's not to say that it can't change over time and in fact if you give it enough time it probably will, but in a significant fraction of patients it doesn't and so why give them treatment for something that is causing them no symptoms and won't impact the natural history of their disease. However if a low risk patient has symptoms, so you're still low risk but you have symptoms you're getting transfusions those patients should get treatment. I won't go into detail about what treatments are available. We can talk about that in the question and answer period, but in high risk MDS whether you have treatment or not... whether you have symptoms or not you should get treatment. Why is that? Well, there's one drug that's been shown to make people live longer with high risk MDS and that's 5-Azacytidine or Vidaza and so it's a medication that is sort of the first line drug for patients who have high risk MDS. It's given seven days out of a 28 day cycle. The biggest side effects are constipation which is usually controllable and unfortunately it can make your counts go down before they go up again. It works in about half the people and when it works it lasts usually about nine months before it stops working.

The last thing I'll say is that having said that about Vidaza, I would say that everybody with MDS should strongly consider clinical trials. There's data that shows that if you get on a clinical trial no matter what it is you live longer for a variety of reasons that we can discuss, number one, 2) even though Vidaza is a good drug the stark reality of MDS is that there's nothing that we know of that cures this except for a bone marrow transplant and that has its own issues and problems that we can discuss as well.

So, with that I'll open it up to any questions.

**Q1:** I have a question about Vidaza. I have low risk MDS, but I get two units of blood every two weeks. So now, March 7, I'm supposed to be starting on Vidaza. Now, you mentioned it's for high risk MDS because that's what I read, but I do have the low risk and I have iron overload because of all the blood transfusions. I have the negative antibodies that you were talking about. So, that's what I was going to try next because I tried plenty of clinical trials. So, what you're saying... I'm a little confused now.

**Dr. Eric Padron:** So, just to summarize your question. You have symptoms, you get transfusions, but you still have low risk and your doctor recommended Vidaza. Why would he do that if I just said it was for high risk? So, I didn't necessarily go over what treatments I would recommend for low risk. It's just if you have high risk the one that you should really strongly consider is Vidaza because, again, it makes people live longer. However, if you have low risk disease there are FDA approved agents and many studies that show that in those patients these

drugs can work, too, and there's three FDA approved drugs for MDS. They include Vidaza, Dacogen and a drug called Revlimid, Lenalidomide, and so those are your sort of three options that are available to you as not part of a clinical trial and so you said you tried Revlimid and it didn't work and so I think that's very appropriate to try Revlimid first. It helps in people who don't have this chromosome change called deletion 5Q in about 30 percent of cases and then after that Vidaza is a very good option. It can improve blood counts in about 40 percent of people and that even though the sort of no brainer indication is for high risk disease, the other no brainer indication is for patients who have transfusion dependent anemia and have low risk disease because we know Vidaza can change that in about 40 percent of people. So, it's not necessarily that Vidaza shouldn't be given in low risk. It just now treatment should be given in low risk patients who have no symptoms. So, I think Vidaza is appropriate. One thing I don't know if I mentioned this, but it takes about three months to work.

**Q1:** Four to six cycles?

**Dr. Eric Padron:** Right. In about 15 percent of people it can take even up to six months to start working and so I do think it's an appropriate choice and I hope that it helps you.

**Q2:** Can you remind us what the difference is between high risk and low risk?

**Dr. Eric Padron:** Yeah. So, there's a lot of ways to skin this cat. So basically, what we mean by low risk and high risk are what are the patients with MDS that we can based on our best guess say that you're going to behave either benignly or your disease is going to behave more aggressively and there are a lot of prognostic models. So, we impute things like your counts, your blasts percentages, your cytogenetic abnormalities, anything that are genetic mutations to assign you to a group and the most commonly used prognostic model is called the International Prognostic Scoring System or the IPSS. There's a revised version of that that we use routinely in our clinic and so based on that model which includes the things that I just now mentioned, you can be allotted to one of four groups: Low risk, Intermediate 1, Intermediate 2 and High Risk and by convention we just say that people who have low risk disease are those that fell into the Low and Intermediate 1 group and those who have higher risk disease are those that were in the Intermediate 2 or High group.

**Q3:** You mentioned three medications – Vidaza, Dacogen and what was the other one?

**Dr. Eric Padron:** Revlimid.

**Q3:** Revlimid. I've been on the Dacogen now for a year and it's working, but does that eventually does the body eventually starts rejecting (inaudible 17:23)?

**Dr. Eric Padron:** So it's not so much that the body starts rejecting it. It's what we think is that your MDS, your leukemic cells, are constantly evolving. It's almost like the way that we're

understanding cancer now it's almost like Darwinian evolution where the environment is your bone marrow and the turtle with the long neck is the cells, the leukemic cells, and so they're capable of acquiring mutations, changing even marks on the DNA and then because it's constantly being treated with this, you basically select out for a resistant clone and in that way Dacogen in almost everybody has a point where it no longer works and so it isn't that your body rejects it or that you have terrible side effects is that the cancer itself learns to grow despite it.

**Q3:** Having said that can you switch to a different, say go from Dacogen and Vidaza? Is the effects going to be the same?

**Dr. Eric Padron:** Great question and so Vidaza and Dacogen as far as we know are very similar drugs. They both do roughly the same thing which is help remove methyl groups on cytosine which is a technical term, but basically it helps turn genes back on that should be turned on and so because they have very similar mechanism of action, it's very rare that a patient who had Dacogen, failed Dacogen, will now respond to Vidaza. I usually tell my patients the chances of that happening are probably about 10 percent or so and I do want to mention, I'm sorry, before... another drug that I forgot to talk about in low risk is Erythropoietin and it really should be the first line drug because in patients who have a low EPO level which can be easily checked when you go see your doctor. The response rates for anemia can be quite high and the side effects are very low. So, Erythropoietin is another one of those drugs that's approved for the use in MDS and other things. So, that's something else. There's a variety of them. The protein is called Erythropoietin, but the drug names are Procrit or Aranesp.

**Q4:** So, (inaudible 19:40).

**Dr. Eric Padron:** Correct.

**Q4:** If you have low red cells.

**Dr. Eric Padron:** That's right.

**Q4:** Okay.

**Q5:** What is the (inaudible 19:46) experience of RARS with Aranesp?

**Dr. Eric Padron:** So, first of all what is RARS? So, RARS describes an entity that has a very interesting appearance under the microscope and what it is that the blood cells that are destined to become red blood cells, they're called erythroid progenitors have a unique deposition of iron around them. It looks like a little ring. So, it stands for refractory anemia with ring sideroblasts and what has been described in the last five years is that they're associated with a mutation called SF3B1 which is actually a favorable mutation. It's actually better to have this mutation in terms of how long patients live and their transformation to leukemia. So, there's a lot of research

going on to identify SF3B1 inhibitors. There's companies that are just beginning to put trials on for that. There's already a drug out there that is being recruited for patients who have ring sideroblasts. It's open here at Moffitt. It's called Luspatercept. So, that's a clinical trial open at Moffitt for patients with ring sideroblasts who have not received Vidaza and Lenalidomide. As far as the response rates to active agents, you should expect, even Erythropoietin, it doesn't really determine a response to Erythropoietin to more than the Erythropoietin level. So even if you RARS the important number is what's your EPO level. Is your EPO level is less than 500, you're likely to respond.

**Q6:** I had a few more questions about Vidaza. My husband has finished his second course of Vidaza, two months of therapy, and my first question... I have a few questions. My first question is that you mentioned that the course of treatment is seven days out of the 28 day cycle and is there a known variation to that treatment because he's been treated for five days in his 28 day cycle. My second is if you're looking for a response from Vidaza, you mentioned and someone else, I think, in the audience did as well that you have to wait four to six months is just following the blood work what's diagnostic as to whether there's a response or do you need to have another bone marrow biopsy and my last question is when you mentioned nine months that if it works it usually lasts for nine months. Does that mean for nine months you don't need to be on the drug any longer?

**Dr. Eric Padron:** All very good questions. So, the first question was regarding the schedule. So, there actually are and so the reason I say seven days is because for higher risk MDS the pivotal clinical trial that showed that it makes people live longer use seven days. Now, there have been subsequent studies that have used five days and show that the response rates to improving blood counts, for instance, are equivalent. So what I usually do is if someone has higher risk MDS, I try and do the seven days, but there are practical reasons why that couldn't happen. Here at Moffitt you can do it because we're open seven days a week, but sometimes in the community you're not and so a typical regimen is five days on, two days off and then two days back on and that has been shown to pharmacologically equivalent. The five days, though, I do do routinely on patients who have low risk disease who don't have high risk disease but have symptoms. So, your second question was...

**Q6:** (Inaudible 23:18).

**Dr. Eric Padron:** What do you look for? So, yeah. So, what do I look for someone who has... who I have on Vidaza? So, if they have high risk disease so you're monitoring their counts relatively frequently because remember I said it goes down before it goes back up again, but so you're going to get blood counts probably every week if you don't do it already at least for the first couple of cycles to sort of get a pace of how the drop is and it's just like almost any chemo where it's after about 14 days or so to go down and then go back up again and then if you have high risk disease, though, I typically in most patients do a bone marrow biopsy after their second cycle not because I expect things to dramatically improve by then because I want to make sure

that it isn't taking off to acute leukemia. So in my practice, I usually try and do that just to make sure we haven't taken off and if things look okay then we're just waiting and looking at the blood counts to see if we find that response and then your third question is if you respond can you be off of it and the answer is you cannot be off of it and so one of the things about Vidaza is you have to stay relatively strict to a schedule especially early on. So, we've seen patients who... and life happens so if you can't for very important reasons you can't, but if you can you really got to stick to the schedule because if you start spreading it out, you could lose a response that you otherwise would have had and it's not one of those things where I'm going to take three months off and then restart it and it's going to work again. It's almost like breeding out selective or resistant clones. If you're giving the cancer just a little bit of it so it gets a taste for it you're essentially breeding out the clone that is going to be resistant. So, you got to stick to it. Now, the average is nine months, but I've had people who have responded for three years. It's a bell curve. So, there are really exceptional responders and in people who have responded exceptionally we do tend to spread it out. Someone wants to go on a cruise or a long vacation five – six weeks, one time is okay even five weeks after a long time it's okay, but early on it really is important to stick to it.

**Q6:** Thank you.

**Dr. Eric Padron:** You're welcome. Yeah?

**Q7:** (inaudible 25:34). Now she's 34. I think we getting (inaudible 25:42). What do you recommend for her? What kind of treatment and what if you say that in my... Well, you said that maybe she wasn't born like that. I don't know. Doctors they think she was born like that and we want to get ready for a bone marrow transplant, an allogenic. Her sister is a perfect match, but what if her sister has the syndrome and it hasn't developed yet because it's you said it would be common at the third age.

**Dr. Eric Padron:** Excellent question. So, what hospital are you treated at?

**Q7:** Oh. We've been around. We are from South America from Ecuador, but we've been around U Health, Sylvester Cancer. We're heading to NIH in Washington. They're going to examine her and her sister, but we don't know what to expect.

**Dr. Eric Padron:** Excellent question and so I may have forgotten to, but I usually when I say that I say 99.9 percent of the time it's not hereditary. So, pediatric Myelodysplastic Syndrome is exceedingly rare as you guys, obviously, know already and the biology is slightly different. There are some mutations like in genes called RUNX1, GATA1 that are associated with familial MDS, but the thing about having familial MDS is not only knowing the genetics but knowing a family tree. So, you can ask yourself did anybody in my family have this disorder before me and it's usually a fairly penetrant disease. So, it's not something that's necessarily going to skip a generation. So, probably more importantly because we don't know everything about the genetics



of these types of diseases. We're trying to, but we don't know everything and so more important than doing genetic screening and that type of thing is really doing a very detailed pedigree analysis with a genetic counselor to determine if they feel strongly enough that there's a chance that this could be hereditary and then the question that you have about your sister is a very relevant one. Could it be possible that she has the same genetic change, but it's still latent in her and that certainly is the case. There's been a case reports where there's been fraternal twins that have been transplanted that have... or I'm sorry, identical twins that have a similar scenario occurring. Now having said that, when I asked you what hospital are you work there are Moffitt and other hospitals, large hospitals, have the capacity to sequence the entire genome of not only her, but her sister and it's not a guaranteed test, but at least it could give you some estimate of okay we found this in here, but it's okay. We didn't find that in your sister. That's not really guaranteeing anything, but it may give you some comfort. I think the most important thing to do is to go back, get genetic counseling and determine if there's any risk of this being hereditary because even in children the majority of people to acquire it, but you're right. You don't fit in the mold. It's a different entity, pediatric MDS, than the adult MDS that most people in the room have. Does that answer your question a little bit?

**Q7:** Yes, but the (inaudible 29:22) two years ago and he says she (inaudible 29:25). Do you think it could be emotional that she developed the syndrome?

**Dr. Eric Padron:** No. No. No.

**Q7:** Too early?

**Dr. Eric Padron:** No, I don't think so.

**Q7:** No?

**Dr. Eric Padron:** I don't think so. I think the question of why her father passed away is very important and if it was on her father's side...

**Q7:** It was a work related accident.

**Dr. Eric Padron:** Oh, I see. So, it wasn't related to MDS...

**Q7:** No.

**Dr. Eric Padron:** ... or anything like that. I don't think so. I don't think that there was any dramatic change of this would have happened when she was 70 and now because of that event although obviously horrible, it happened this early. I don't think so.

**Q7:** Okay. Thank you.

**Dr. Eric Padron:** Okay. Any other questions?

**Q8:** Procrit and Aranesp, is that how you say it? Okay. Anyway. I got the MDS. I got it, I think, from chemo and radiation and I took a series of shots, it's about 18 shots over six months and my oncologist down in Naples said because the numbers didn't bounce back up. It didn't seem like it was doing much of anything. Do you agree with that? That's half the question.

**Dr. Eric Padron:** Oh, absolutely.

**Q8:** So then we figure well, let's try this Aranesp. So, I tried a half a dozen shots of that at the, I guess, it's 200 milligrams and just everything kept still declining because I kept a log of the whole thing and now I'm in the 300 milligram and I got one shot more with that and that seems to be doing something. Now, I guess there's other things that could happen, too, but...

**Dr. Eric Padron:** That's not unusual because many patients... So, one of the things you should look out for is sometimes patients will be discontinued from Erythropoietin because it didn't work at a lower dose. For instance, Procrit at 40,000 units it doesn't work and you're doing it every other week. Well, we really recommend that you go up to the highest, the 60,000 units every week, really give that a good shot before you say it doesn't work because as we said there is a limit amount of agents that we can use here. So, you really have to maximize each one and it is certainly the case that we see patients who are on a lower dose of Erythropoietin agents that aren't responding and then at a higher dose start to respond.

**Q8:** Is it the higher dose than 300 of this (inaudible 31:55)

**Dr. Eric Padron:** Yeah.

**Q9:** Our son is 45 years old. He was diagnosed four years ago. His biggest problem is platelets and based on bruising that he experienced before his diagnosis he thinks this may have gone on a decade prior to that. So, he apparently acquired very young and has been living with it fairly well, but his hematologist in Indianapolis where he lives and the folks at City of Hope where he eventually if they find a match will do a bone marrow transplant have been bickering back and forth about treatments for the low platelet count. Are there any recognized treatments to address the platelet issue independent of the MDS?

**Dr. Eric Padron:** Well, I would say that they're not independent. The MDS is the cause of the low platelet counts and so if you are lucky enough to be a responder to Vidaza or Dacogen, you can potentially have an improvement in platelets. Now, outside of those there are clinical trials that are particularly looking at platelets. So, we had one I believe is just closed here with an agent called Eltrombopag or Promacta and that drug is FDA approved for another platelet disorder called ITP, but they're testing it in MDS with some promising results and so there are

drugs in clinical trial like that that are being tested in Myelodysplastic Syndrome that we expect would preferentially impact low platelets.

**Q9:** Thank you.

**Q10:** Could you repeat those the clinical trial for low platelets?

**Dr. Eric Padron:** Eltrombopag is the name of the drug. Eltrombopag.

**Q10:** And by platelets, by how low do you have to be for something like that?

**Dr. Eric Padron:** Either, I believe, the inclusion criteria are that you have to be either below 50,000... don't quote me on that, but below 50,000 or transfusion dependent.

**Q10:** Okay. I am also low platelets for the person there and was diagnosed five years ago and I also have low whites. I'm totally neutropenic.

**Dr. Eric Padron:** But remember like if just sort of to give some context, we're talking about... in the platelets we're talking about people who are getting to the point where they will need transfusions or already there because we have many more platelets than we need and so if you still have low risk MDS then the fact that we still watch people who have no symptoms remains true. So even if you have a platelet count of 70,000. So, the bottom line of being normal, say, is 150. If yours are 70,000, you aren't expected to have any symptoms. You should be okay. You can even get some types of surgeries done and so in those patients we still may elect not to treat them. So just your platelet count is low doesn't necessarily mean that you need treatment right away. The same thing is true for the white count because the part of the white count that's most important for fighting infection is called the neutrophil. Those are really very, very rarely improve with Vidaza or Dacogen. Even in patients who are complete responders, it's very rare to see people improve their neutrophil count and so for that reason it's not something we typically jump on. The sort of silver lining is that unlike other diseases for reasons we can talk about later people with MDS generally it happens for sure, but generally aren't those that get serious recurrent infections while they're on treatments like Vidaza. They can for sure receive it for sure, but as a general rule even if you're neutropenic if you're smart, if you wash your hands, if you use common sense you can be... you can do fairly well without a treatment for your neutrophils.

**Q10:** Okay. Thank you.

**Q11:** What was the name of that clinical trial drug for the RARS?

**Dr. Eric Padron:** Luspatercept. I'll write it down for you after the...

**Q11:** My other question...

**Dr. Eric Padron:** I probably can't spell it. I have to write it. I can't spell it.

**Q11:** The other question I have is bone marrow biopsies. How frequently should a patient be getting biopsied?

**Dr. Eric Padron:** So it depends on the clinical scenario. Obviously to diagnose MDS, we require a bone marrow biopsy. We're doing research hopefully to do that in your blood eventually, but right now you need a bone marrow biopsy and then if you're starting a treatment you kind of want to have a bone marrow biopsy within 30 to 60 days so you know what your baseline is because it's hard to say if things are working if you're working off a marrow from two years ago and then every time you're starting a new treatment. So at the very minimum, that's the frequency. So in some people it can be very infrequent.

**Q11:** If they're on Aranesp, I mean, is having it once a year too much?

**Dr. Eric Padron:** Performing the bone marrow biopsy won't impact the disease at all. It'll just be uncomfortable. I don't think I can argue with doing it once a year, but it's also very appropriate not to do it and so you do your bone marrow biopsy, you take your Aranesp, your counts get better and they stay better for two, three, four years. We're not expecting much change in the bone marrow, so we're not going to go looking for something. We're going to just wait for your counts to change and then at that point do a bone marrow, but I don't think it's wrong to do every year. If you were saying I was getting it every couple of months and your counts are stable then no, you probably don't need that.

**Q11:** My concern is that he might be taking out good bone marrow.

**Dr. Eric Padron:** No, you're not. You're just sampling a very small amount of what is your entire skeletal system. So, you're okay.

**Q12:** I have a question about cytogenetics and I specifically would like to hear more about the deletion of 5Q and if it's combined with monosomy 7 as well.

**Dr. Eric Padron:** Okay. So, the most common cytogenic abnormality in Myelodysplastic Syndrome is the deletion of 5Q. Now when the deletion of 5Q is seen as the only abnormality in your cytogenetics and you have well defined criteria which most people with that abnormality do that is normal platelet counts, severe anemia and certain bone marrow changes, you have then what's called the 5Q- syndrome and in that context based on work that my mentor did who works here in Moffitt, Alan List, he showed that patients with that deletion can have dramatic responses to Revlimid, that Lenalidomide drug. So in that context, you expect to have transfusion independence not needing transfusions for a long time for a couple years even in about 70 percent of cases. So, and that's also a syndrome that's usually more indolent. So, it's

one of the cytogenetic abnormalities that are good to have. Now, the story changes when you start getting the acquisition of additional cytogenetic events. So, monosomy 7 in general is one of those bad cytogenetic events and in combination with del 5Q, it's no longer the 5Q-syndrome. Now, there is data that shows that if you have the del 5Q plus only one, you still may have a decent response to Lenalidomide, but the caveat here is not to get too technical, but you want to do that in low risk disease because there's no study that shows that even if it's Lenalidomide, even if you have del 5Q that if you have high risk disease it's going to change anything and that's a something that we see coming in from the community every now and then is patients who have del 5Q, monosomy 7, Trisomy 8, a whole long line of cytogenetic abnormalities and because they have the del 5Q they were put on Lenalidomide but I would argue that what's more important is all that complexity that makes them high risk and so in that case you do Vidaza.

**Q13:** Is it common to have the three lines low?

**Dr. Eric Padron:** Very common. You mean, hemoglobin, platelets and white cells?

**Q13:** Yeah.

**Dr. Eric Padron:** Yeah. It's part of the disease is to have what's called pancytopenia. So all the three lines are low.

**Q13:** And the neutrophils, they're the worst.

**Dr. Eric Padron:** The neutrophils, not necessarily.

**Q13:** She's got very low count of neutrophils.

**Dr. Eric Padron:** No, I mean in general, there isn't one of the counts that I would say is the worst. It's very individualized. Some people who have low counts if only you could get their anemia better, they will feel so much better. There's some people who have platelets that are really low and that constantly have nose bleeds and if only you can improve the platelets they feel so much better and then there's rare people who have chronic infections with MDS and if only you can improve their white count, but most people with MDS are okay with the neutrophils low. So, I wouldn't necessarily say it's the worse, but it's very individualized. It depends on the person and what is bothering them the most.

**Q14:** Most of us that are treated at research centers we give a lot of blood and I guess that would spin out (inaudible 41:52) could you explain in the laymen language just what are they looking for?

**Dr. Eric Padron:** I get that question a lot. Why are you taking so much blood? Don't you know I don't have any?

(Laughing)

**Dr. Eric Padron:** We get that a lot and so a couple of things. So first of all you may notice that when they're taking out your blood there's different color tubes that they put them in. Those tubes denote what is actually coding... Those colors denote what's actually coding the tubes and so some of them are coded with something called heparin, some of them are coded with something called EDTA. Some are coded with nothing and depending on what they're coded with allows them to be used for a variety of different (inaudible 42:30) and so that's why they need a sort of variety of tubes and then we just do a lot of tests and so one thing that we do our lab does a lot is sequencing a lot of your genes to look at prognosis to help us potentially define something to target and so we do that and then lastly Moffitt Cancer Center has something called the total cancer care protocol which is across cancers and essentially if you as a patient consent to it allows researchers like myself in the lab to use your blood or bone marrow samples which would otherwise have been discarded to do research and peripheral blood unless you have very high risk MDS, we don't necessarily get stem cells from that, but we get a lot of other valuable cells that we can use to test new drugs in animals. In my lab, we have a model where we take your or someone like you's blood and actually inject it into a mouse and then give drugs to that mouse to see if the leukemia goes away and so those are the types of things we can do with the blood that you give us.

**Q15:** (inaudible 43:37) you consider monosomy 7 is a sole abnormality.

**Dr. Eric Padron:** It's one of the cytogenetic abnormalities which is significant by itself. It does connote a more aggressive type of disease.

**Q16:** A lot of transfusions, 471. Recently...

**Dr. Eric Padron:** Is that a record?

**Q16:** I don't know if it's a record, but that's what I got. Anyway, recently Hep C has showed up and so they just tested me last week it came back with Hep C 1B. I wonder what the 1B is.

**Dr. Eric Padron:** I'm not the right guy to ask. What it probably is is just like all of us there's genetic variants of these viruses. So, I bet it's a genetic variant of Hepatitis C and it probably infectious disease doctors dictate what type of antiviral therapy you should get.

**Q16:** Well, I was told it was not the definition of it, but it was very rare like 1 in a million and when the doctor told me that I said, "Well, I must be special."

**Dr. Eric Padron:** I'm sure you are.

**Q16:** Well anyway, I don't know what it is.

**Dr. Eric Padron:** That would be my best guess. That's certainly not my area of expertise though.

**Q16:** Okay. Thank you.

**Q17:** On Aranesp and Procrit you said there were the three different categories. So, what category do those shots fall in of the three, I don't know, the scientific names or something, Vidaza and there were three that you original talked...

**Dr. Eric Padron:** The Procrit is the Erythropoietin. The EPO shot. All it really is is so it's kind of our body has been wired a little bit weird. We wouldn't expect this maybe. I don't know or maybe you would have, but actually it's our kidneys that tell our bone marrow when to make more blood. Our kidneys make something called Erythropoietin. That's why people on dialysis are anemic because they don't have this erythropoietin and, in fact, they give this to dialysis patients routinely and so all this medication scientific name is is someone in the lab, now a very rich pharmaceutical company now made a synthetic form of that protein and so not surprisingly if you have low levels of that protein in your body and you have low risk disease you're likely to respond. If your levels are already high like many patients with MDS, we know the likelihood of you responding to it is very low because it's already there and it's not doing anything. So, all that is is basically the protein that your kidneys are supposed to make to stimulate your bone marrow to make more blood.

**Q17:** And Aranesp does the same thing?

**Dr. Eric Padron:** Yes.

**Q17:** And is it okay to... like I had Aranesp shots for over a year and then I was traveling and they said that they didn't have Aranesp and they gave me Procrit instead. Does that matter?

**Dr. Eric Padron:** It shouldn't. It shouldn't matter. That being said, I mean, things happen, but if one is working don't rock the boat. Stay with that one.

**Q17:** (inaudible 47:05) and they said that they couldn't give... that they didn't have Aranesp in the area and that probably had to do with the drug companies.

**Dr. Eric Padron:** Or it could be some of these things need to be received from a specialty pharmacy and so there's always practical issues of why things can't be perfect, but I'm just saying in an ideal world you just want to stick with the same one if it's working. That's all.

**Q18:** (inaudible 47:33).

**Dr. Eric Padron:** It's not FDA approved. It's a very exciting drug in clinic trial. It's available at Moffitt as part of the clinical trial. If you are interested in just so you don't make a trip and then be disappointed. You can't have had Vidaza or Revlimid. You could have had EPO, Aranesp or Procrit, but not those two.

**Q18:** (inaudible 47:56)

**Dr. Eric Padron:** The design of the study. It's not like it may or may not work, but usually when they do clinical studies they want to test it in a clinically homogenous group of people. Hopefully if this study works it's FDA approved, it's not to say that it wouldn't be available for people that have had Vidaza.

**Q18:** I'll assume (inaudible 48:20).

**Dr. Eric Padron:** It's hard to say. Not in the immediate near term. I don't think in the next 12 months for sure, but hopefully soon.

**Q19:** (inaudible 48:32) some wonderful things in the *New York Times* about breakthroughs in...

**Dr. Eric Padron:** Immunotherapy.

**Q19:** Yeah.

**Dr. Eric Padron:** So no doubt. So, I'll speak a little bit about immunotherapy in MDS and then we can talk about what areas are of interest now. So, immunotherapy has been no doubt a breakthrough in cancer. There's drugs called checkpoint inhibitors that take the brake off your immune cells, the T cells and allow them to attack your tumor and it's been revolutionary in diseases like melanoma and lung cancer, cancers of the kidney, Hodgkin's disease and probably many others in the future. There are studies for sure at Moffitt Cancer Center and other places testing checkpoint inhibitors in Myelodysplastic Syndrome as well. As yet there is no data that suggests that it will augment the immune systems efficient to impact MDS, but the studies are ongoing. There's been one interesting abstract at ASH that I found of note that I actually have a patient where we tried this on. In patients who have had a transplant and then unfortunately relapse there was a very provocative study out of Hopkins that showed in those people they tested 12 people and five of the 12 had a complete response by giving them this checkpoint inhibitor. So, very preliminary. Has a lot of risk associated in that context, but that's the one scenario that I know is reported and has some promise. Far as research in general, so there's a lot of us working really hard to find the next Vidaza or the next Revlimid and I would say a couple of things. So in high risk disease, virtually all of the clinical trials now for better or worse are



asking the question in combination. So, what is the combination that we can add to Vidaza to make it work better, to make it last longer? There's also an oral form of Vidaza that's being tested. So, it's not a shot anymore. It has advantages in that it actually not only would be more convenient because it's a pill, but actually may work in people who fail the shot and so that's in clinical trial as well. It's also about to be available at Moffitt Cancer Center as a clinical trial and so in high risk I would say those. There's the checkpoint inhibitor studies and then in low risk something that we're interested in here in Moffitt Cancer Center is using or inhibiting a different arm of the immune system. So rather than what's called the adaptive immune system with T cells, it's the innate immune system. So, the sort of infiltry of immunity. Labs here at Moffitt have shown that those cells are really up regulated in the bone marrow of low risk MDS patients and that if you remove them they start making more blood that so somehow this innate immune system is being hijacked and suppressing your blood production and so there's a whole variety of trials trying to target these cells. Some of them are called myeloid derive suppressor cells and there's a series of clinical trials here at Moffitt trying to target those as well.

**Q20:** A couple years ago I heard Dr. (inaudible 51:57) from the University of Florida. He mentioned that they were doing research on the bark of a willow tree from South Africa. He thought would be significant as far as MDS is concerned. Have you heard anything about that research?

**Dr. Eric Padron:** Nope. Sorry. I just don't know.

**Q20:** Okay.

**Q21:** You were talking about Vidaza so much. What determines whether they give you Vidaza or you get Aranesp shots? I mean, I'm not understanding the...

**Dr. Eric Padron:** Good question. So in high risk disease, in my opinion, you get Vidaza because it's the only drug that shown to make you live longer. So low risk disease is a little bit more complicated. You've got a menu choice. So if you look at things like the NCCN guidelines which is a body of representatives from cancer centers like Moffitt and Dana-Farber and Hopkins all getting together and asking what is the best way to treat patients. If you look at those guidelines and if you look at how we do it here the first thing you want to do is see if your EPO level is low because if it is I think Procrit's number one because it's... That EPO level, remember that stuff that's made in your kidney, if that's low then one of the Procrit or Aranesp or one of those derivatives is your best bet. If it's not low then the second thing we look at is there are markers that have been shown to make you more likely to respond to immune suppression with a combination of drugs called ATG and cyclosporine. We do it here at Moffitt in a subset of patients and in some people it really works. It's a five day hospitalization and then you go home and see if it works. It sometimes takes up to six months. So, those are the sort of things we check first because we know that they can work in the right people. If you have the del 5Q syndrome and you need medicine because you're transfusion dependent or anemic then you

go Revlimid. If you don't have the del 5Q syndrome then you really have a menued style option. You can do any of the three reasonably. Here in our center because of data that Dr. Karachi has published, we find that if you do Revlimid first all things being equal. There's obviously individual things that have to be taken into account that then the response rate to Vidaza later seems to be held the same. Whereas if you flip it around and do Vidaza first, Revlimid doesn't seem to work as well. Now, that's sort of a general statement and you really have to talk to your doctor about why they select one versus the other, but in our experience all things being equal in that context we would do Revlimid and then Vidaza or Dacogen.

**Q22:** (inaudible 54:39) Vidaza causes chest wounds (inaudible 54:44) in patients who have received Vidaza who have mild heart attacks.

**Dr. Eric Padron:** So when you do clinical studies you have to report anything that happens to those patients appropriately so and as I mentioned many of the patients are anemic and so I would say in my opinion that I know of no data that definitively links increased risk of cardiovascular events to Vidaza. Perhaps it could be a function of the disease because those people are anemic as well. So, it's not a very common side effect seen. The most common are constipation and lowering your blood counts, but it certainly conceivable that if your blood counts are lowered even more by Vidaza that you could get at risk for having a heart attack if you're so anemic. So in that context it's possible, but I know also of no research specifically geared to answering that question because I really don't think it's fundamentally linked to Vidaza.

**Q23:** (inaudible 55:55) unit in Boca Raton, Boca, and seeing Dr. Karachi here every three months. I've been treated with the Procrit every week. When you hit the top of Procrit would you suggest going to one of these clinical trials or Vidaza. Also does a mitral valve insufficiency of 40 percent enter into it?

**Dr. Eric Padron:** What do you mean by hitting the top? Do you mean like it doesn't work anymore?

**Q23:** When Procrit stops working.

**Dr. Eric Padron:** Oh, yeah. No, absolutely.

**Q23:** Which way do you go? Do you want a clinical trials or Vidaza? We just did a bone marrow yesterday. I was just saw him yesterday. So, that may decide.

**Dr. Eric Padron:** If you have those ring sideroblasts, I'm sure Dr. Karachi will talk to you about the Luspatercept study because you couldn't have... You know, it's all about sequencing it in a smart way. So, you want to make sure you have the most options for you available. So if there's

a clinical trial that's really exciting, but you can't have Vidaza or Revlimid and you're the perfect candidate for it, I think it's a no brainer.

**Q23:** Have to wait two weeks for his results of the bone marrow.

**Dr. Eric Padron:** Yeah. I mean, you're in very good hands.

**Q23:** But does mitral valve insufficiency have any...?

**Dr. Eric Padron:** Not unless it's... Usually the language of a clinical trial is you can't have a concurrent illness that's life-threatening. So if you have rage (inaudible 57:14) mitral valve insufficiency and there's a life expectancy of six months for that then no, but if it's just a problem you have then that's okay usually.

**Q23:** Thank you.

**Dr. Eric Padron:** I think you had a question.

**Q24:** Do the counts, your blood counts, determine whether you go on a medication like Vidaza or whatever as opposed to just Aranesp and blood transfusions?

**Dr. Eric Padron:** The EPO does the... determines whether you should go on Aranesp or not, EPO level, and the number of transfusions. So, a low EPO level and low number of transfusions, good candidate.

You had a quick question.

**Q25:** I'm not sure what I understood about (inaudible 57:55) form of Vidaza (inaudible 57:56) anything (inaudible 57:57) clinical trial and if it would be a clinical trial would be open to someone who's (inaudible 58:02) by injection before?

**Dr. Eric Padron:** Yes. Yes and yes.

**Q26:** You mentioned about the oral form of Vidaza. Has there been any mention of doing the same with Dacogen?

**Dr. Eric Padron:** Not to my knowledge.

**Q27:** This is more of a practical question. Maybe half the people here are Medicare patients. Are you aware that there are certain medications that are in trial, but I at least had been told that unless I was blood transfusion dependent I would not be able to get reimbursed by Medicare.

**Dr. Eric Padron:** For the clinical trial...

**Q27:** I would have to be on transfusions to be able to receive that particular drug. Otherwise, they wouldn't cover it.

**Dr. Eric Padron:** And you're talking about a clinical trial?

**Q27:** Yeah.

**Dr. Eric Padron:** So the way that a clinical trial reimbursement works is that say I have a clinical trial. We meet with the budget office here at Moffitt and I decide as a principal investigator what I deem to be standard of care and what is experimental. Everything that's standard of care, I think it's the Clinton Administration that passed this law. Everything that's standard of care, your insurance company is on the hook for. Anything that's experimental including the cost of the drug or any additional test that, for instance, I or someone else who runs a study would deem to be outside of standard of care is the responsibility of the sponsoring agent usually the pharmaceutical company. That's the generalities. I'm not sure why you had your particular problem, but that's how it works.

**Q28:** With the Vidaza because a friend of mine was on the Vidaza and he had a very bad experience and he's trying to talk me out of going on it. He immediately needed to have a bone marrow transplant. If it doesn't work, Vidaza, what are... does it go into AML or...?

**Dr. Eric Padron:** A very good question. So first off, I mean, there's always a balance and you guys probably are aware of this more than I am between well-meaning friends that want to tell you about their anecdote and making an informed decision overall. So, of course, like having someone that's been through it has been an incredible resource, but also I think you have to look at it... you don't have the same type of MDS that that person had. Having said that though there is emerging data for sure that after you receive and you fail it, the disease can become more aggressive. That is for sure. It can. Absolutely, but of course that should not preclude you from trying it given that it's one of the only few agents available and then in about half of the people you can have a dramatic response for a long time, but it is certainly the case in my sort of anecdotal experience and in some literature that states that it appears that in some cases Vidaza after it stops working for whatever period of time that was the disease can behave more aggressively. It's not clear whether that's because Vidaza is doing something or it's just the disease progressing naturally.

**Q28:** Now, Revlimid didn't work on me. Would that be an indicator? Did you say something about Vidaza and Revlimid? Revlimid did not work on me (inaudible 1:01:44) chromosome. Would that be an indicator as to Vidaza would be a good...?

**Dr. Eric Padron:** We don't think so. We think you probably are okay in terms of the chances of your responding to Vidaza. If it was the other way around that's why I was saying we have some literature that states that maybe your chances of responding to Revlimid would be lower after Vidaza, but the other way around we think is okay.

I know there's a question back here.

**Q29:** I've read everywhere of the leukemia risk. What would be for her the risk and after the allogenic bone marrow transplant before. Would there be any risk still?

**Dr. Eric Padron:** Yeah. So, the risk for everybody with MDS is about 30 percent of people and that's in the adult population. I just don't think that there's enough people with pediatric MDS that they've looked at the overall rate of transformation and, frankly, you would expect perhaps maybe a little higher because you have so much more time. The average age of somebody diagnosed with MDS is 70. So, there's only 20 – 30 years at max that the disease can evolve whereas in your case the disease can evolve much more time. I don't know an exact number. I don't know if there is an exact number, but for all MDS patients it's about 30 percent and then you can sort of personalize what that chance of transformation would be based on the individual factors, the genetic mutations, the chromosomes that type of thing. As far as before or after transplant there's no doubt that the transplant itself can dramatically reduce the risk not only of the leukemia coming back, but of the whole disease coming back for sure. It's not zero though and in fact, so people can and do relapse after a bone marrow transplant. In general, the younger you are the better you do with these bone marrow transplants and I really hope that happens for you, but in older patients they can relapse.

**Q30:** (inaudible 1:03:50) relapse with a little less treatment (inaudible 1:03:58) a transplant, but it's not as severe. I just had a friend go through that and she...

**Dr. Eric Padron:** You're talking about something called the DLI, a donor lymphocyte infusion.

**Q30:** Yes.

**Dr. Eric Padron:** But I wouldn't characterize it as usually. It can happen whereby you can control the disease after and then try a donor lymphocyte infusion, but it's not common that you can get to that point. After it relapses after transplant, there are a lot of clinical trials that are being tested like the one that I mentioned with the checkpoint inhibitors. So, there are a lot of new things that we can try but it certainly shouldn't be characterized as something that can be quickly put back into remission.

**Q31:** (inaudible 1:04:42) Would it be possible, but not today. I'm looking for a second opinion and (inaudible 1:04:49) cancer down in Naples, but just to see if everything is what they're telling me.

**Dr. Eric Padron:** That's what we're here for.

**Q31:** Who would I see about that later on?

**Dr. Eric Padron:** I don't know. Maybe you can E-mail me or someone and I'll put you in touch with the right person.

**Q32:** (inaudible 1:05:13)

**Dr. Eric Padron:** So, we have two of them from two different companies. That's one of the strategies that we're using to deplete the cells that I was talking about that are part of the innate immunity that we think are suppressing your blood production and so they have that CD33 marker on them and so these antibodies sort of flag them to be destroyed. That's the theory.

**Q32:** Thank you.

**Q33:** You talked about these genetic mutations. This is all (inaudible 1:05:49) a new field for a lot... It is for me anyway, what those genetic mutation markers mean. Did those change? I mean, I have a certain genetic marker right now, a mutation. Is that likely to evolve into some other... I mean, of this disease, evolve so strangely. Am I likely... you know, I had a blood test last week, have one marker and then a year from now have a different one?

**Dr. Eric Padron:** Absolutely. So what we think happens is that when your disease is sort of clinically stable, the repertoire of mutations you have and the clones that define them are probably stable, but...

**Q32:** (inaudible 1:06:35)

**Dr. Eric Padron:** Oh, yeah. In any cancer including MDS, it's what's called an allogal (sp?) clonal disease. So there are almost assuredly at least a few clones in there and then probably dozens if not many more sort of the percolating at the bottom and so those are what's thought to be the (inaudible 1:06:59) for resistance for progression and that type of clinical change is what then we think is associated with the acquisition of mutation. So if you get a lot of therapy and you do better and then it comes back again usually it comes back with what we call the founding mutation, the one that first started everything, but additional ones that weren't observable before and that...

**Q32:** Dr. List mentioned there was like 55 mutations that you guys are looking at related or... I don't understand all that.

**Dr. Eric Padron:** So our Moffitt panel looks at 52 genes that are... have been associated to be mutated in, say, five percent or more of MDS patients. Now, the problem with mutations in MDS is that there is a peak of genes that are mutated in 30 or 40 percent of cases, but there's a very long tail. So, there's a lot of mutations that occur in patients at very low frequencies. So, even with 52 genes, we're not capturing every single gene that you can possibly have mutated, but that's okay because we don't know what the significance is of every possible gene you can have mutated. We're working on identifying what that means, but we think that in our panel we get the ones in most cases we know what to do with.

**Q33:** And that helps you identify the treatment?

**Dr. Eric Padron:** Almost never it does actually. Not yet, but we check anyway because there's some mutations have, for instance, we check a mutation called BRAF and it's mutated in less than one percent of patients with MDS. Well, why would we check it? Because there's actually a very potent BRAF inhibitor that's FDA approved for melanoma because in melanoma that mutation happens in 50 percent of the time. So, it's worth it to us to check it because if we find that one person we can now give them this drug assuming the insurance company says okay which is a big assumption and then they have a very high likelihood of that working. That's so called drug repurposing. We can use... by finding these events, but in the future I'm sure we'll find others that happen very infrequently, but if we find them it's important enough to check.

**Q34:** The knowledge of this in (inaudible 1:09:12) my country is very poor. We had to come here six years ago and she was diagnosed here and I would like to know what's the difference between... we had to take the option of NIH because we don't have insurance. We have nothing and they offer us a trial where she's going to be with 49 people. I don't know. What do you think about that? Would it make any difference between that trial or if I could have one for her just for her because they say she's not common. They're going to go and look for the common things and not for her because she's a rare case.

**Dr. Eric Padron:** So in general, every... there's virtually never what is called an N=1 clinical trial. So every clinical trial has many patients on them and part of the clinical trial is to identify what are the characteristics of a patient which make them more likely to respond to the drug being tested. In the case of NIH, I have a patient just like you guys as well. He's a little older. He's 40 years old. He's from Nicaragua and he basically is doing the same thing. He's going to the NIH as part of a study where they're testing the ways in which you can give a transplant and in that way they can facilitate giving you a transplant. I think it's a great option. Obviously, they're one of the better centers where you can get that type of care and like I said the stigma of going on a clinical trial, being sort of the last resort and being a guinea pig just really isn't the truth. There's studies that show that if you are on a clinical trial you live longer, all things being equal. It's because you're monitored more closely, you're at a big medical center where they kind of see this all the time. They go this is a really rare disease and this is kind of all I see, all my colleagues see, all Dr. Karachi, Dr. List, that's all we see. So, for all of those reasons it's not

a bad thing to be on a clinical trial and it's very well regulated and in some cases we wonder if it's over regulated, but we have to go through the FDA, we have to go through scientific review committees, ethic committees, a whole list of committees that takes about on average six months from the start of the submitting the clinical trial to finally getting it approved. So, I encourage everyone including yourself to enroll in a clinical trial.

**Q34:** Thank you.

**Dr. Eric Padron:** Do you have a question?

**Q35:** Yes. The gentleman talked about when you talked about 52... was it 52 genes? Okay. By the genes and you said usually it never helps to determine the treatment that you pick, but the genes versus like the cytogenetics does that... do the cytogenetics is that the same thing or is that something different, the chromosomes?

**Dr. Eric Padron:** So, the chromosomes are genetic changes on a more macro level. So you have big chromosomes that are being either deleted or fused together where they shouldn't be and the gene mutations is looking at individual genes and saying are those individual genes mutated.

**Q35:** So, they are different.

**Dr. Eric Padron:** They are different, but the general concept is the same. Right now we're at an era in cancer medicine where we have a lot more data with respect to genetics than we know right now what to do with. So, what we have all the data, but we only know what to do with a handful of those with respect to treatment, but for instance like Luspatercept or other clinical trials where it was first tried on everybody with MDS and found that people with ring sideroblasts or SF3B1 mutation actually do better. The same thing may be true for the next gene mutation that we check routinely and don't know yet what to do with.

**Q36:** You're seeing MDS in its still fairly rare form in itself and then isn't there like five different categories of MDS?

**Dr. Eric Padron:** So, Myelodysplastic Syndrome is a disease and it is classified in a bunch of different ways and you're right. By the World Health Organization, there's a list of, which by the way is about to be revised, of ways that we sort of call it and based on how a pathologist looks at it under the microscope. There's ways that we group it by prognostics. We say well you have lower risk or higher risk. There's ways that we do it by your genetic defect, del 5Q. You have SF3B1 mutation. You have... So, there's a lot of ways to chop it up, but in and of itself it's one disease that rises in incidence by at least 10 fold as we age.



**Q36:** I guess what I'm getting at is that since there are like five different categories of MDS, RARS being one of them, are the treatments different depending on which type of MDS you have?

**Dr. Eric Padron:** Not necessarily. I would say the biggest sort of chasm in how you treat MDS it's the lower and higher risk. So, that's the most important thing to know. Are you the lower risk or are you the high risk? All of them, obviously, have some degree of importance otherwise we wouldn't do it, but if you had to say what's the most important thing for me to know about mine, am I lower risk or am I higher risk.

**Q37:** One question that I had in relation to... I was treated with Methotrexate for a number of years for lupus and one of the side effects of the methotrexate is the possibility of damaging the bone marrow. Could that have possibly started this?

**Dr. Eric Padron:** It's not one of the common ones, but I guess it's conceivably possible.

**Q38:** (inaudible 1:15:31) clinical trials (inaudible) does it require that you're really more or less on site to use it (inaudible 1:15:39) or does it vary and is there a contact person if you'd like more information?

**Dr. Eric Padron:** So, it does vary and so that there's some clinical trials that have, for instance, that they're testing pills that you just have to come once a month. I would say the least frequent that you have to come is once a month and there are trials that you have to come very frequently. Some of those trials, actually, the sponsor subsidizes some form of travel and housing for the patients, but that is also not established across the board. So, it does vary and I would say the best contact person would be to come to Moffitt to get a second opinion and have your primary doctor whether it be myself, Dr. List, Dr. Karachi or anybody else sort of help you decide what the portfolio is because there's so many things about what type of MDS you have, how good do your kidneys have to be, how good does your liver have to be that it's difficult for just one person to tell you yeah you should come for this one. So, it should be a conversation between your current doctor, potentially a doctor at Moffitt and you.

**Q39:** (inaudible 1:17:01) There was a question about insurance and what we found was initially we had Humana as a supplement to Medicare and it limited the doctors that we could see and we found United Healthcare through AARP, the supplement, it's about \$240 a month, I think, but he gets excellent care here at Moffitt and he doesn't pay anything. There were a couple of medication, the Jadenu, for iron buildup and Thalidomide that were like experimental or wouldn't be covered and Moffitt put us in touch with a foundation that short of the 240 a month, I had to pay anything. So, insurance is important.

**Dr. Eric Padron:** So, I think we're about 15 minutes over. I'll be back for lunch and I know Sarah Tinsley who seen tons and tons of MDS patients and is a great resource is going to give you guys a talk and then I'll be back for lunch if you guys have any more questions. Okay?

(Applause)

**Sara Tinsley:** How's everybody feeling? Hungry? Not after breakfast.

So, my name is Sara Tinsley. I'm a nurse practitioner. I work here at Moffitt for a long time, the past 25 years and I've been taking care of patients with Myelodysplastic Syndrome and AML and different hematologic disorders and I'm going to be presenting part of the information that's in your *Building Blocks of Hope* book if you can locate that. It's the next one. This is the book we're going to go over part of if we can locate it.

So, we're going to talk about how you live with MDS. This was a book that Sandra Curtain and the International Nursing Leadership Board for the MDS Foundation developed. This is a representation of 31 different nurses in 12 different countries. You can see it's from all over the world and I want to thank you for attending today. It was a wonderful question and answer session with Dr. Pedron. I'm glad that you were able to ask him your questions about your specific type of MDS and treatments that are coming down the line and we do have an electronic evaluation survey that's available if you brought an electronic device, an iPhone or an iPad. If you'll remember to complete that after we're all finished and if you don't have an electronic device, we also have paper surveys available and there are different ways you can support the MDS Foundation. If you're interesting in being involved you can text MDS to 41444.

So when to start treatment. This was covered many of you asked questions that were related to this. So when do we start disease modifying treatments? If a person is requiring transfusion with packed red blood cells or you have blood counts that are changing like you have a decreasing white blood cell count, decreasing hemoglobin, decreasing platelet count then that would be an indication that you may need to start therapy or if when you have a bone marrow biopsy an aspiration. If you have high risk disease and your blasts are increased that is an indication to start treatment.

So what are increased blasts? Have you all heard this term and what are blasts? They're very immature cells and the more blasts you have then the more like leukemia your MDS becomes. So, they crowd out your bone marrow's ability to make your normal cells and when it evolves from MDS into AML, the trigger for that is when you go from having less than 20 percent blasts to 20 percent blasts or more. That's this by definition cutoff. When you get to 20 percent or more then you've crossed that line where they call you MDS. Now, you're AML when it's more than 20 percent and so a lot of our therapies when you're treated with Azacitidine the goal when you're starting for higher risk MDS is to decrease the percentage of blast to have a more normal blast percentage. Normal is less than five percent. So, the higher the blast, the higher you are in

the MDS like high risk disease and we individualize treatment which is, I think, what you were hearing Dr. Pedron try to address with each of you as you told him the unique features of your disease, but not only exactly what type of MDS or what type of cytogenetic abnormalities or if you have a certain mutation we look at you as a person and what is your performance status. Are you able to do most of your activities by yourself independently? Are you able to do the things that you used to do? Are you fit or are you becoming frail and then tailor our therapy and our recommendations to meet your needs and what's going on in your life.

So as he said, we stage MDS with different classification systems. The most commonly used is this IPSS-R and this is called the International Prognostic Scoring System and there's a revised category, but we have lower risk disease and when you have lower risk disease like if you have refractory anemia or a refractory anemia with ring sideroblasts or you only have anemia and you don't have increased blasts in your marrow then that's usually someone who has more of a lower risk disease and so when we treat you what we're trying to do is improve your body's ability to make your normal cells or improve hematopoiesis. So if you're requiring transfusion with packed red blood cells on a rather frequent basis then when we treat you we're looking to improve or decrease the number of transfusions that you need so that you don't run into problems with iron overload which you can get when you get lots of transfusions.

When we treat higher risk disease normally that's a person who has increased blasts in the bone marrow or if you have multiple chromosomal abnormalities in your bone marrow or if you have ones that we know are associated with higher risk disease like deletion of 7Q or monosomy 7 then that would be like a higher risk disease and what you're really trying to prevent in that case is that person's MDS changing into acute myeloid leukemia. So, you're trying to improve survival and what's key with that is looking at that bone marrow biopsy after you have your four to six cycles of therapy and trying to... and Dr. Pedron says he likes to repeat the bone marrow after two cycles if he's treating higher risk disease that has a lot of blasts in there because he want to make sure that the disease is not getting worse that you haven't transformed into acute myeloid leukemia and so in that case you're trying to improve the blast percentage but also improve survival because once it changes from MDS to AML life expectancy decreases. So, that's what we're trying to do in that case. So, we really do think of MDS into those two different categories, lower risk and higher risk even though we have all those subcategories within there and we think of primary versus secondary and I know some of you know this. What is primary MDS? Yes?

**Q40:** (inaudible 1:26:26)

**Sara Tinsley:** Right. It started on its own and secondary is like if you had another cancer and you received chemotherapy or radiation therapy for that and then as a result the cells in your bone marrow have transformed and become different and they've developed this Myelodysplastic Syndrome from your prior therapy and then we also look at the cytogenetic status and so the way they do cytogenetics they get a karyotype is one way and we also do FISH.

Karyotype is where they take... and that's done from your bone marrow and they take your actively dividing cells and then they take the chromosomes where those cells are actively dividing and they line them up and we have 23 pairs of chromosomes and we have our sex chromosomes. You may have seen the "23andMe" on TV and they talk about you having chromosomes. We're looking at the chromosomes of the bone marrow cells and they look at 20 cells and then they see if there are any structural abnormalities in those chromosomes and like you heard Dr. Pedron talking about there's deletion of the long arm of chromosome five and that's the most common chromosomal or cytogenetic abnormality and that's called deletion of 5Q. We can also have the 7, monosomy 7, where all of 7 is deleted or parts of chromosome 7 and you can see those. They look like... Well, it depends on if the karyotype is done well. Sometimes they look like little gummy bears or Xs kind of lined up if you see a picture of them and you'll see them, 23, and you'll see like pieces of them missing. They actually give you a picture a lot of times or there's a description of them and they'll have in brackets how many cells they tested and so if they have 20 that means they've tested 20 cells. Sometimes they aren't able to get all 20. So, another way we can look at cytogenetics is by if you can't get dividing cells on your bone marrow aspirate, the liquid part of your bone marrow, then we can test your chromosomes by looking at a test called FISH or fluorescence in situ hybridization. Big words and you have to tell them what you're FISHing for. So when we're taking care of MDS patients we're FISHing for MDS abnormalities and you don't have to have a bone marrow to FISH for MDS. They can take it off of a blood sample and try to see what kind of... They usually will test specific probes using different colors and so they can see if there's translocations. They can see if there's deletion of 5Q, if there's deletion of 5Q... I mean, 7Q. They look at the most common chromosomal abnormalities associated with MDS, but you have to tell them which ones you're looking for. So, it has its pros and cons. It can tell you those specific ones that you test for, but if there's unusual chromosomal abnormalities then you have to really look at the bone marrow aspirate to get that result.

Does anyone have questions on that? Yes.

**Q41:** So what is the cytogenetic status tell us? It's a risk category?

**Sara Tinsley:** Yes. You have to know what your cytogenetics are in order to be able to plug in the information on the International Prognostic Scoring System. To be able to stage your MDS you have to know what your cytogenetics are because that's one of the things that gives you a zero, a .5, a 1 or a 1.5 and then you add those all together and you'll know whether you're low risk, Intermediate 1, Intermediate 2, High Risk or Very High Risk. So, you have to know your cytogenetics to know whether you're low or high risk.

And then when we're looking at treatment choices we also look at lifestyle. How do you live? Do you like to travel and how does this treatment impact on your ability to travel? If you have lower risk disease and you're okay with getting transfusions if you need transfusions every two weeks then you get to make a choice that you can go somewhere and get a transfusion and

maybe still travel versus starting a therapy that you have to stick to a every four to five week schedule at the same location. Sometimes we can through the MDS Foundation try to arrange for other centers to help you out when you're traveling. So, just remember that and then the patient's personal choice. If you just know that you don't want to go down that route like if bone marrow transplant's recommended for you and that's something you know you would never want to do I have patients that just say no way I'm not going to do that even if they know the alternative is that their life is limited.

So, the key principles of therapy in MDS. We know that the only potential cure is allogeneic bone marrow transplant, but like we talked it's not an option for many patients. We look at the age. Comorbidities means what other illnesses do you have and do you have something that's so... that is impacting on your ability to live a long life more than the MDS is. Like if you have heart failure or if you have severe cardiomyopathy or weakening of your heart muscle to where a transplant would be too risky for you or the other thing that can happen is transplant's not an option for people because you don't have a donor in the registry. You either don't have a sibling that matches your HLA typing. That's what they look for. They do HLA typing of your blood and then they look to see if your siblings match and if your siblings don't match then they look in the registry and not everyone can find a donor, but we really emphasize that age should not dictate whether you could have active therapies. It's more are you fit or are you frail and you could argue if you're fit enough and you want to be treated then you should be treated for your MDS and not just look at the age and I do have... I see patients in their 90s that are still getting therapy and I see some patients that are not very old at all that are not well enough to be treated. So, we don't treat just based on age.

And as we talked about all active therapies require time to work and it's not like a sprint. This is going to be like a marathon like something you just have to work with and try to... and that's why this book should be helpful for you because it's trying to live and still enjoy the things that you enjoy while having a diagnosis of Myelodysplastic Syndrome and trying to structure your treatments and your life to where those kind of interact instead of you're not able to do anything you enjoy anymore. For both Lenalidomide and for Azacitidine and Decitabine, those all take four to six months before you know if they're going to work and I have seen some patients that have stable disease at six months and we went onto eight months and then they had a response. So, you can have some early responders and some late responders even with our therapy. I would like to make mention also that all of our clinical trials in treating Myelodysplastic Syndrome are structured in the same way meaning that you wouldn't expect to see a wonderful response like in the first month. Those clinical trials have certain points like at the four month mark where we look at the bone marrow again to see if it's helping you. So, it's not just for the FDA approved therapies but therapies that we're testing for the future that we would expect time to be an element of helping these work and also the blood counts with these treatments get worse before they get better. Have any of you experienced that? Yes. They get worse before they get better. So, you might need more transfusions of blood. You may have never needed a platelet transfusion before, but in those first two cycles of Azacitidine or Lenalidomide it's not

uncommon that you would need an increase in your transfusion requirements and maybe you were never neutropenic and then suddenly became neutropenic. So, that doesn't mean that you failed the therapy. It means it takes time to work and this is what we expect and setting those expectations, I think, helps.

So why is time required? Well, you have to consider what's happening. Before your treatment begins... these are your blood counts down here and that's a red cell. This is a white cell and these, I think, are supposed to be platelets here although I'm not sure. Maybe that's a platelet. They're little dots, but your blood counts drop as the MDS progresses and your normal blood cells are crowded out by these abnormal or dysplastic stem cells in the bone marrow in the blood and then you can see your blood counts taking a hit here where there's not many cells in here either abnormally looking or normal looking. There's just not a lot of cells there and if you look over here at this graph, on this... on the Y axis here these are... this is absolute neutrophil count. So, those are your infection fighting cells and we think less than one is considered neutropenic and you can see the intervals here are 1.2, 1.7, 2.2. So and down across the bottom are weeks of therapy. So, you can see how this gets worse here in these first four cycles even down to the sixth... not cycles. I mean, weeks... down to the sixth week and then you can see right around 11 weeks of treatment how things get better and stay up there on the neutrophil count.

And as the patient begins to respond, your bone marrow begins to recover. You see there's more cells in here and that's allowing your marrow to make healthy blood cells and the counts continue to improve as you get more normally functioning cells in that bone marrow replaced by those dysplastic cells and then as you continue to get treatment you can be weaned from packed red blood cells transfusions and that's if it's working. That's what you should see around four to six months of treatment.

And so during this time right here I think is when I see patients really needing more support. We take them from getting their labs checked every month to we put in for a weekly lab check so we can see what's going on. You might need prophylactic antibiotics. You may need transfusions of packed red blood cells. You may need a platelet transfusion. Normally, there are different cutoffs for transfusions of packed red blood cells. They do have recommendations by the blood bank that they put out, but we really try to individualize it meaning that we don't just go by a number, but go by the symptoms associated with anemia which means if you're having a difficult time walking because your hemoglobin is low or you have shortness of breath and just trying to do very small activities or you just can't get anything done then that would be an indication that you could need a blood transfusion and with platelets the main problem that you run into is the risk for bleeding. So when platelet count is less than 50,000 you want to be careful what type of over the counter medications you use and also when you're neutropenic and that's in your *Building Blocks of Hope* book also in the Staying Well section which is in Section Five. You want to look at any of the nonsteroidal anti-inflammatory drugs, aspirin, Advil, Ibuprofen, Napricin, Naproxen. All of those make your platelets not stick together, so you would want to be careful and not use those unless you have a cardiac condition. Sometimes they would still recommend

aspirin if your platelets up until they're less than 30, but you want to be careful with those because that can be like two things working against you as far as making it... putting you at risk for bleeding.

So, the key principle of therapy time's required for your best response, minimum of four to six months. Cytopenias are low blood counts, get worse before they get better and so some of the strategies we use during the first couple of cycles is we can do dose modifications although we try to stick with the original dose, 75 milligrams per metered squared. For higher risk MDS and try to give it on schedule and the reason is is you're trying to decrease those blasts in the bone marrow. So, you really want to try to stick to that schedule. Of course, sometimes people can get a severe infection or other reasons that you have to delay, but we do try to stay on schedule more.

Supportive care. We mentioned this. Transfusions of packed red blood cells and platelets or prophylactic antibiotics and different physicians have different philosophies on that. If you've had problems with specific types of infections then if you become neutropenic that might be something they put you on to try to prevent you from getting an infection. Other physicians like to wait and see if you have any problems before they add another medication especially if you have a high copay or things like that.

Does anybody have questions? It's all quiet.

This is an example of trilineage means all three cell lines – white blood cells, red blood cells and platelets. So, trilineage means all of those different types of cells that are made in your marrow, whites, reds and platelets respond following four cycles of Azacitidine and so down across the bottom you'll see June and September and October 2010 and then over here you'll see hemoglobin or white blood cells and you can see in the beginning things got worse, but now this person has had a really good response. It looks like the hemoglobin's up around 12, but down in here it was in the eights. So, this was in the beginning of the treatment. They bottomed out and then came back up and then the yellow line represents the platelet count and you'll need to look over here for the platelets because those come in 20, 40, 60, 80, 100 and really a normal platelet count is around 143 to 350 on our labs. So, these are not in the normal range, but definitely a more functional platelet count, more on this fourth cycle of therapy and this is at day 100 you can see where things get better and they were lowest here in these first two cycles.

And then this is not a typical response. We learned that from Dr. Pedron, but we both... we all have in our clinics people who don't respond and people who have a very prolonged response, more than we would think and we always want to be in that group that has like that response to Azacitidine for 9 or 10 years and I've seen people like that they just keep having a response and this is a lady that Sandy Curtin takes care of and she's had a response for over 10 years with Lenalidomide. So, she started treatment in 2002 and this goes up through 2011 and, again, the hemoglobin is this pink up in here. So, you can see she started out like at a 7.5 hemoglobin and

now she's running after many years up in the 12 and 13 gram range, but Lenalidomide it helps your red cells, but it lowers the white blood cells and the platelet count and that's what you see here is that the platelets are running around 100 now and in the beginning when she first started it looked like she was around 60s and you can see that initially her platelet count was up around 200,000. So, this is what we see when the patients are on Lenalidomide. You get the hemoglobin increasing, but the platelets decrease and the white blood cell count decreases, but it should fall out around at a functional type of blood count to where you're out running into peoples with infection or bleeding and you do modify the dose based on what's going on with the blood counts especially in the first two cycles. You can hold it and then restart like if the neutrophils drop less than 500. Another side effect that's associated with Lenalidomide is rash. So, you have to at certain times if the rash is too severe you hold it and then restart when the rash decreases.

So, what can I do to stay healthy? This is in your Staying Well section which I think is chapter five in your *Building Blocks of Hope*. With Myelodysplastic Syndrome many times we don't know what happened to bring it on unless you had prior radiation or chemotherapy for another cancer and you can't really... you don't really have a lot of control about what your disease does in your bone marrow. You can't like just tell your bone marrow to be better and it'll be better.

So, what can you do? Well, you can modify your lifestyle to try to do change the things that you have of over like a balanced diet. When I first became a nurse, we used to tell people during treatment to take it easy. Don't get up too much. Just, you know, just take it easy. Well, now we know that if you don't... you'd think we knew it then I haven't been a nurse that long. If you don't use it, you lose it and there have been many studies that show that fatigue which is the most common symptom for all cancers and MDS is no exception. Fatigue is the biggest symptom and there are studies showing that moderate activity or it might be even light activity depending on where you're starting. That can help with the fatigue and I know it's like one of those things. Well, I'm too tired to get started, but if you can just set small goals if you're really having a hard time with fatigue and try to do a little bit more every day to try to actively work to maintain your level of functioning and I know many of you do this already. Avoid infection. I saw hand gels out there. So, this being implemented I know. Avoiding sick people. Sometimes that's hard especially if they're people you love and avoiding bleeding. If you're working in the kitchen, gloves if you need to if you're doing a lot of cutting and if you get a cut and it doesn't stop bleeding and your platelets are low you would want to call your healthcare provider. You might need a transfusion with platelets, but the first thing you would want to do is hold pressure and if it's your hand you can put it above your head. That'll help minimize bleeding, but definitely seek medical attention if you have low platelet count and you're experiencing bleeding. Also if you have a fall and hit your head when your platelets are less than 50 that's a reason to seek medication evaluation because you can bleed inside your head if your platelets are really low and you can't see that until if you start getting really... become unconscious or something like that. So, just be careful and try to do and continue to enjoy the things you love and keep living. Get enough rest.



And take advantage of the available resources. You have packets with you, the *Building Blocks of Hope* has information in there that could help you and reach out to your family and friends and you want to be an active participant and building your own hope and then if you'll turn to your chapter five in your book, you'll see there's an MDS Manager and you're already actively participating in this because one of the first *Building Blocks of Hope* is understanding your disease and so you're all doing that by being... showing up today on a Saturday morning when it's cold outside. So, everybody gets a yay for you. Know your IPSS and the IPSS Revised risk category to know what potential therapies are available for you. Ask your physician or nurse practitioner or nurse to review your cytogenetic abnormalities with you. I'm happy to do that with patients I see. If they want to know about it to go over what kind of chromosome problems you have and also those mutation proof profiles. We do those on all of the patients now and we can see the unique characteristics of your disease and you can Google on [clinicaltrials.gov](http://clinicaltrials.gov) for different clinical trials that are available. You want to ask questions about your treatment, the schedule, possible side effects and what we plan to do for you as a healthcare provider to help you get through your therapy and also consider lifestyle and transportation. I encourage people to come with a friend if they're just starting a new treatment because you don't know if that's going to be a really hard day for you. Are you going to through your day easily, but it's nice to have someone there for support and then become a partner in your MDS journey and you can track your progress. In your booklet there's sheets for monitoring your bloodwork, monitoring your treatment, writing down your bone marrow biopsy results. It doesn't have a place for your mutations, genetic mutations. That's how fast the field is evolving. Like three years ago we didn't do mutation profiles on everybody, but now we are.

So understanding your diagnosis will help you and your caregiver take an active part in your therapy. You can go through these different tools that allow you to track and manage your journey and you might want to make copies of them or I think on the website you can download them. I'm not sure and just make you could print extra copies of the tracking plan.

And there's also a mobile application for this that has professional and personal contact all in one place. There's a symptom tracker. That's really helpful for me if you bring your symptoms, a list of the symptoms that you're experiencing so that I can appreciate what your problems are and try to actively do what I can to help you manage your symptoms. Even if it's just fatigue we can go over how much sleep are you getting, are you having a hard time sleeping at night, are you a snorer, do you have sleep apnea. If you try to look at the whole picture are you getting enough hydration? Dehydration leads to fatigue or do you have an infection or something else going on. So if you keep track of your symptoms, you want to keep a list of your medications with reminders and this is all on the mobile application and there's also a tutorial if you are really working with your iPhone. We have like a full computer at our fingertips. Yes?

**Q42:** Well, this morning I went to the Android Play Store and tried to find this mobile app and I can't. Do you know where that's located or what (inaudible 1:53:23) certain word to get to it?

**Susan Hogan:** Mobile app almost (inaudible 1:53:31), but it's not (inaudible). So check (inaudible)

**Sara Tinsley:** There you go.

**Q43:** (inaudible 1:53:45)

**Sara Tinsley:** Not yet, but it's almost there. So, soon to come. You think within the next couple of months. Yes. We've been working on this the *Building Blocks of Hope* book and the app for several years. So, it's a work in progress. Thank you for telling me that. I looked for it last night, but I thought it was just me and sometimes you can't tell if it's you or it's something else. So, thanks a lot.

And then there's also someone on the questions that Dee sent me was looking for support with other people because they feel like this journey with MDS is kind of lonely and there are virtual support network out there, but you need a Google account and they have tailored information based on your specific IPSS-R. So, that means low risk MDS is with low risk and high risk is with high risk or you know, so that because you... it is quite different. I have low risk patients that I've been seeing since 2004 and they get just get transfused every two weeks and they go on about their business. The white counts normal, platelets normal. I have some MDS patients that I've been following since 2004 that I just look at their bloodwork. So, there's lots of different flavors of MDS. So, this will be great if you can hook up with or connect... I guess I shouldn't say hook up. You can connect with someone that's at the same stage of the diagnosis that you are and personalized symptom management support, which I think that's very helpful because sometimes you don't know if it's just you or this is common for everybody and I can tell you for sure that fatigue is number one for all patients or for like 95 percent of the patients that I see. Even the ones that are just in being monitoring. I'm just monitoring their blood counts. They still have problems with fatigue. So if I could come up with a good solution for fatigue, I would be rich and there would be a lot of happy patients. That would be the more important part.

And then, again, the Patient Outreach and Advocacy programs. You could contact Audrey Hassan. She has a toll free number and she E-mails me, too, and asks me questions about... and tells me about events that are available for patients and that's her E-mail. So, she's very responsive to your communication.

**Q44:** Where's that in our book?

**Sara Tinsley:** The slides. I don't think you have all of the slides in your book, but the chapter five of your *Building Blocks of Hope*. Do we have the patient liaison information on one of the handouts?

**Q44:** If anybody finds it (inaudible 1:57:16)

**Q45:** What's on the disk we received?

**Sara Tinsley:** I haven't looked at this.

**Q45:** So, it's not your slides.

**Sara Tinsley:** No, it's not my slides. That's a good point. So, you might want to write this down. So if you're interested in an outreach program, but if you call the MDS Foundation they can connect you with Audrey very easily.

So, let's talk about you. Any questions? Yes.

**Q46:** Not about me, but you know the workshop coming up on transplants and they mention a phone conference. How exactly does that work?

**Sara Tinsley:** She's asking about a conference on transplant. Is that through the MDS Foundation?

**Q46:** You have to register by March 2<sup>nd</sup>.

**Audrey Hassan:** Transplant. I don't know (inaudible 1:58:42) Foundation.

**Sara Tinsley:** I don't know.

?: Speak with Audrey. That's who with...

**Q47:** Audrey's information is on page seven of book six.

**Sara Tinsley:** Page seven of books six is Audrey's information. Thank you very much.

**Dee:** (inaudible 1:59:14) that evaluation sheet. If they could just turn it back over to me or they can get it online. I'm going to send them the link to it on Monday, the evaluation sheet.

**Sara Tinsley:** And Dee said she's going to send you the link for the evaluation on Monday or if you can fill it out in your... electronically.

**Dee:** Right. If you don't want to fill it out with this paper, but if you decide to fill it out, write it out, just hand it back to me when you come back from lunch or before you go to lunch.

**Sara Tinsley:** There's one question. Yes? Either one?

**Q48:** No, just (inaudible 1:59:53). My husband (inaudible) I don't like (inaudible) anywhere.

**Sara Tinsley:** Well, the booklet has a lot of the information in it even in a more detailed like what can you eat, where can you go, how do you...

**Q48:** Okay.

**Dee:** Make sure I get your name.

**Q48:** I will.

**Sara Tinsley:** So, Dee's sending slides if you want them. Yes?

**Q49:** You mentioned that "23andMe."

**Sara Tinsley:** "23andMe." Yes.

**Q49:** Is there anything... Would that be any benefit to us that we would learn anything different than we would normally get from our blood test and that kind of thing?

**Sara Tinsley:** I think the "23andMe" tells you more about your ancestry like your background. I haven't personally used it, but I do know some of the physicians have used it just to figure out like where they came from like if they're not sure about their remote history. I don't think it would help... I don't see how it would help with your MDS. You know, like figuring that out unless you found like there was something familial like Dr. Pedron was talking about where they do the pedigree with the geneticist where they go back and look and see if for several generations there's been an MDS or some kind of blood disorder. So, I guess in that way it could help you connect with people more in your remote history that you might not be aware of.

**Q49:** Is that something kind of... I don't know... something that you might like to know? Is it worth the \$200?

**Sara Tinsley:** I don't know it cost \$200. I just saw the commercials all the time.

**Q49:** As I recall, it was \$199, but...

**Sara Tinsley:** It sounds like a lot of money.

**Q49:** That's what I'm thinking.

**Sara Tinsley:** Yeah. For that, I mean, I don't think that you'll get information that would help us with your treatment at all. Really. I can't see that because we're doing myeloid mutation panels

and even that information although it helps us understand your disease more it doesn't really help us for the most part tailor your therapy unless you had a mutation that we have a specific drug developed for.

**Q49:** Okay. Thank you.

**Sara Tinsley:** Like a JAK mutation or he said like the BRAF mutation or one of those, but that's a small percentage of the mutations.

**Q49:** Thank you.

**Q50:** Would it help if you were looking at a bone marrow transplant?

**Sara Tinsley:** I don't think so because they only... when they're looking at the National Marrow Registry, they are testing your HLA typing against everyone who signed up and they do it by computer. So, it used to be a lot more difficult, but they can tell within a couple of weeks if there's a marrow... if there's a person who has signed up for Be the Match that matches your HLA typing. Yes?

**Q51:** Is there an age limit on being a bone marrow donor?

**Sara Tinsley:** That's a good question.

**Q51:** I signed up to be a...

**Sara Tinsley:** There's an age limit.

**Q52:** We were told that it's 55.

**Q53:** I was told it was 60.

**Q54:** It's 18 to 60.

**Sara Tinsley:** I do know that if it's a family member like if you're 60 and your siblings are probably in their 60s, they will specifically test them, but if you're trying to go into the registry to be a donor for other people then they'll limit that because I don't know if someone who had MDS that went to AML and I think his 82 year old sister was his donor which was amazing to me and did okay because you usually start losing stem cells as you age also. So for them to be able to collect that number of stem cells.

Alright. Well, thank a lot, everyone, and I wish you the best of luck on your journey and there's lots of resources and support out there and just let me know. I work here. My E-mail is available if there's anything I can do to help you I'd be happy to.

(Applause)

(General chat 2:04:32 – 2:05:18)

**Q55:** (inaudible 2:05:17).

**Sara Tinsley:** I work at Moffitt, Moffitt Cancer Center. Our clinic's just across the way. You ask about seeing him.

**Q55:** (inaudible 2:05:26) and me, we just don't get along.

**Sara Tinsley:** You could call... I can give you the phone number for our clinic and they have a new patient appointment center. Let me see if I can find that for you because you can refer yourself, too. You don't have to be referred.

**Q55:** (inaudible 2:05:51) computers and E-mails and stuff... I'm just looking at how he could get an appointment here.

**Dr. Eric Padron:** Before I left, I know people had additional questions and I'm done eating, so if you guys want to fire away we can ask some more questions.

**Q56:** Is iron overload a problem if you're getting routine platelet transfusions as opposed to whole blood or hemoglobin or whatever she was talking about.

**Sara Tinsley:** Packed red blood cells run into problems with iron overload.

**Q56:** Right.

**Sara Tinsley:** But not for platelets.

**Dr. Eric Padron:** We'll have a talk at 2:30 if you want to know more about iron overload. So, Sara and I both answered questions for you. So again, just fire away.

**Sara Tinsley:** The one problem with platelets is if you get transfused with platelets quite a bit. You can become refractory to platelets, too, but you don't have problems with the iron overload and they'll know if a person's becoming... and refractory to platelets means that when you get a platelet transfusion, you don't get a good bump or an increase in the platelets and so the way they would know if you're becoming refractory is if they do a post platelet count and you're like

7,000 on the platelets before you got the platelets and then afterwards you were 5. That would mean that didn't help you at all. Like you destroyed the platelets that we just gave you and so that's one of the strategies if they notice that you're not getting good bumps, they can do post platelet counts and then give you more specialized platelets specific for you. They can cross match for platelets and things like that.

**Q58:** Sara, I'm pretty sure I'm in a low risk category and I've been through three different clinical studies. Now, we're talking about going to Vidaza for me and did I hear doctor say that there's an instance of Vidaza after that getting to a more aggressive strain of MDS?

**Sara Tinsley:** He has low risk MDS. I know him well because he's been on several of our clinical trials and now he's considering going on the trial that's using... comparing the three day Vidaza versus five day versus Decitabine and he wants to know if it can make his disease worse. Is that right?

**Q58:** Yes.

**Dr. Eric Padron:** The evidence that speaks to that is not very robust, but I would say anecdotally and perhaps that's why Dr. Karachi and Dr. Garcia-Manero at MD Anderson are looking at the question of three days versus five days versus Dacogen because maybe perhaps you get the same effect with perhaps less toxicity down the road, but there is nonetheless evidence that after you fail Vidaza the disease can become more aggressive, but what is not clear is does Vidaza play a role in that occurring or is it just a matter of the people that are being treated with Vidaza have... are prime to be more aggressive because you're treating them for a reason and then after they progress through Vidaza that manifests and perhaps you can make an argument that would manifest with any disease you give... or any treatment you give that patient. So, it's not yet clear if there's a cause and effect, but it is true that after you fail Vidaza the disease generally can become more aggressive. Does that help?

**Q58:** Yeah (inaudible 2:10:44). Does that hold true with Dacogen?

**Dr. Eric Padron:** Yes.

**Q58:** It's the same. How close in similarity are they? (Inaudible 2:10:58)

**Dr. Eric Padron:** So, it's another good question. So structurally, they're very similar and not to get too technical but what they do is on your DNA, your DNA is made up of four letters, A, C, T and G and one of the letters, the C is prone to get marked. So, it's marked by a methyl group and that tells the gene to turn off and so the way that these two drug work is that they target the machinery that puts that mark on and off. So mechanistically, it's thought that they work similarly. Some of the differences though are 1) it's thought that Vidaza goes more into RNA than DNA and it's thought that Dacogen is more DNA than RNA. What the consequences of that

are it's not known. Clinically, some of the differences are, again, Vidaza is really the only drugs that in MDS has shown to improve survival whereas Dacogen is definitely an active drug and some people actually think in the AML subtype it may perhaps even be a bit more active and there are different variations of how you can give Dacogen. Some people give a 10 day induction form of Dacogen and very aggressive MDS and AML that is different than Vidaza. So, there are some subtle differences clinically, but the main point is they're very similar. If you fail one you're unlikely to respond to the other and Vidaza is the only one that improves overall survival that we know improves overall survival.

**Q58:** And a follow up question on that. Known side effects of Vidaza and Dacogen?

**Dr. Eric Padron:** They're very similar.

**Q58:** Do they have any damage to the organs or anything like that?

**Dr. Eric Padron:** So it's not a common occurrence that you have an organ damage from Vidaza or Dacogen. In general what we do is if someone... I'm just making sure I don't get this backwards. If someone has a bad renal failure, we choose Dacogen because it's metabolized through the liver and vice versa, but it's not typically something that harms your organs. The constipation though if you don't catch up to it and if you're not proactive, so that's why I always ask my patients take a stool softener whether they constipated or not on the days that they take their Vidaza can potentially get very severe and so we've seen rarely people get really bad colitis because the constipation just kept getting worse and worse and worse and worse. So, you just got to be careful about the side effects.

**Q59:** On the gene mutations, if you've got a gene mutation that's got a negative prognostic value if you have more than one gene that's got negative values, is it cumulative where it's maybe like twice as bad or is it just bad once?

**Dr. Eric Padron:** Very good question. So, it's a rapidly evolving field, but I'll just tell you the two major points for gene mutations. One is there's one classic paper by colleagues of ours at Boston that showed that if you have any one of five genes mutated that any one of them, one, two, three, four, five of them or just any of those five, your prognosis goes up by one score. It goes from...

**Q59:** I've heard that. You got two of those five or three of those five. Which one higher?

**Dr. Eric Padron:** Right. So, there's recent data from the same group presented at ASH that there is an adverse prognostic factor with number of mutations, but it's not additive or it's not multiplied like you were suggesting. It's not like... if you have one mutation versus five mutations it's five times worse, but it is statistically worse for you to have more and more



mutations with the exception of SF3B1. That's always taken out because that's the only gene that we know when mutated gives a favorable prognosis.

**Q59:** Out of those five, I think I have four.

**Dr. Eric Padron:** And the one that we know is really important is P53.

**Q60:** What's important?

**Dr. Eric Padron:** P53.

**Sara Tinsley:** She wants to know what the five mutations are that you're talking about. Which ones.

**Dr. Eric Padron:** You're quizzing me. ASXL1, P53, RUNX1, EZH2 and ETV6, I believe. Those are the five. ETV6, I believe is the fifth one.

**Sara Tinsley:** It sounds like alphabet soup.

**Dr. Eric Padron:** It does. At the end of the day what matters is that we can check for those. Those are part of the 52 genes that we check here at Moffitt and we mostly take it into account for those patients who are at the borderline because if you go from Low to Intermediate 1, it doesn't really matter. You're still lower risk or if you go from Intermediate 2 to High Risk, you're still High Risk and in the R-IPSS, that revised version, there's an intermediate category. So, it's very low, low, intermediate, high and very high and so in those NCCN guidelines I talked to you about that intermediate group is where mutations are critical because they really help you decide where are you going to bin that patient? Is it in the higher risk or the lower risk? Frankly, the vast majority of the scientific evidence for mutations and their use in the clinic is on prognosis. So, what we're talking about. So, there's a lot of papers talking about how we should implement mutations in prognosis. We just want to see more of those papers and we're working on those two on how to implement mutations and treatment.

**Q61:** How many of those mutations have targets?

**Dr. Eric Padron:** So, as we were talking about earlier. Very few and in fact, in MDS, the only real modified target is deletion of 5Q for Revlimid. The sort of top four mutant genes, TET2, ASXL1, SRF2, SF3B1. At the moment there are no drugs that target those, but remember there's that long tail of mutations that occurs and in there exists sort of a mishmash of mutations that do have targets which were developed for other cancers in which those mutations occur at a much higher frequency. It's like the BRAF mutations. There's also gene fusions that can occur. So, where one gene actually fuses to another one. The classic example of that is in another disease called CML. So, that fusion is... puts together a gene called BCR with a gene called ABL and

essentially is responsible for a patient getting CML and there's a drug called Gleevec that targets that and turns what is a fatal disease into a chronic disease. There are fusions in some of forms of MDS. There's PDGFR fusions that often have sensitivity to Gleevec as well, but those are also opportunities to target if you do sequencing studies.

**Q62:** This might be more of a question from you, but the side effects of getting Vidaza injections locally are pretty painful. We read one thing that applying evening primrose oil might help or not. Is that something you ever suggest to your patients and are there other suggestions just to try to minimize the local discomfort other than taking Tylenol and so on?

**Sara Tinsley:** If someone's having really severe injection site reactions, we have switched them to IV for the Vidaza.

**Q62:** Anything for the reactions locally?

**Sara Tinsley:** Well there is a technique, I don't know if they've used the technique, but it's called the air sandwich technique to where they are supposed to change the needle after they withdraw it so that you don't get any exposure to the medication as it's entering the skin that's supposed to decrease the injection site reactions. So when I get paged from a nurse or I hear that someone's having injection site reactions, I print out the instructions for how to use air sandwich technique and it's basically it's air at the beginning so you don't want the nurse to prime the needle all the way down till they see the medicine. You want to leave air at the end. At the top and at the bottom and the medicine is kind of sandwiched between the air and a fresh needle.

**Q62:** Right. So when they take it from the vial, they should change the needle.

**Sara Tinsley:** Exactly. Change the needle and sometimes that works very well.

**Q62:** Thank you.

**Sara Tinsley:** You're welcome.

**Q63:** What about warm or cold compress or anything like that?

**Sara Tinsley:** I think they recommend not massaging the area or anything like that right afterwards like the package insert, I think, says. I think the concern was if you rub it a lot or if you put ice on it or things like that you can alter the absorption of the medication.

**Q64:** Makes sense.

**Sara Tinsley:** I think that's the concern with that.

**Q65:** Because of many clinical trials are supported by drug manufacturers is the results or the output or the conclusions are they proprietary and held back or are they distributed widely through the medical community so that the benefit is larger?

**Dr. Eric Padron:** Excellent question. So, there are two forms of clinical trials. One, there's a set of clinical trials that are conceived and initiated by the investigator and the institution, so that we have what are called investigator initiated trials at Moffitt where say I have an idea and I pitch it to the company and they pay for it, but it's my idea and my trial, my data. There's also company sponsored trials that it's the company's general idea that institutions also think it's reasonable to do and facilitate and in that case it's their data and so that's where the responsibility lies. In general any positive trial will get published because... but a huge problem in the research community and it's not just the pharmaceutical companies, it's also the investigators is the lack of published negative trials and it's for a lot of reasons. You can envision the reasons the company may elect not to publish a negative trial, but investigators, too, because publishing a study is a lot of hard work and you don't get the credit and the recognition for publishing an active drug that's very positive in that context. So, it's a big problem and there's even some people thinking about starting journals of negative data because it's important to know if a trial didn't work or not. In general, this is a small community. I know all the guys at MD Anderson, at Dana-Farber, at all the big centers that... and we all work together. We actually have a consortium called the Evans Foundation Clinical Consortium where there's six big centers that do clinical trials together. So in general one way or the other we know what the results are of these trials, but for sure positive trials get published, negative trials it's a big problem.

**Q65:** What are the six member (inaudible 2:23:29).

**Dr. Eric Padron:** Moffitt, MD Anderson, Johns Hopkins, Dana-Farber, Cleveland Clinic and Cornell.

**Q66:** Sloan Kettering isn't one of those?

**Dr. Eric Padron:** It's not.

**Q67:** Is Hutchinson?

**Dr. Eric Padron:** No.

Any more questions?

**Sara Tinsley:** No more questions?

**Q68:** (inaudible 2:23:59) he told me that I should do (inaudible) first.

**Sara Tinsley:** She wanted to know about the RUNX1 and was it GATA is the other one?

**Dr. Eric Padron:** Yeah, but like we talked in the break I think it's a very unusual circumstance. So if to answer the question as best as you can whether her sister has the same predisposition as she did would probably require sequencing all the genes of her, her sister and some sort of control like her skin or and her sister's skin which like I told you we can do. So, but it's not some sort of test that is FDA approved or you order it on a sheet of paper. That's under research in my lab. So, we could do it, but it's not like a test you can tell your doctor to write in the community. It's a specialized test at big centers.

**Q69:** (inaudible 2:25:02) very low white blood counts. What are the more typical problem areas to avoid?

**Sara Tinsley:** For someone with a low white count for a long time?

**Q69:** Yes.

**Sara Tinsley:** Usually, if you have neutropenia for a long time you do start to see more unusual type of infections that you could be screened for if you start to develop symptoms like some of the fungal infections. Do you want to add to that?

**Dr. Eric Padron:** Yeah. I mean, like I said earlier I think there are some diseases of low white blood cell count that are characterized by people getting infection after infection after infection. MDS really isn't like that, but again people get infections and I know after saying that someone will raise their hand and say, but me I get a lot of infections. So, it's true that people get infections but in general it's something that can be managed as best as you can it's just a matter of washing your hands at all time and finding... What I always tell my patients is finding the balance between living your life and being cautious and having common sense. So like an example I give is if your grandkids are coming, I don't think it's reasonable not to have grandkids over because that enriches all of your lives and so I think having them over is great, but if one of the grandchildren have some sort of cold you say I'll play with you in a couple weeks. So things like that I think, using common sense make a really big difference and then, of course, getting your flu shot is also important.

**Sara Tinsley:** And I know at the break after... right before lunch, someone was asking me which it comes up all the time in our clinic for someone who's chronically neutropenic do they need to wear a mask all the time and that kind of is... but they get mixed messages which can be unsettling because one doctor tells you you have to wear a mask all the time and then another one says not to.

**Dr. Eric Padron:** Again, it's a balance and what I tell my patients is you don't have to... you're not living in a bubble on the one hand, but on the other hand I can't tell you it'll reduce your risk of infection by this much, but if I was in your shoes and I was in a church where people are coughing or a movie theater, it's not that I wouldn't go to church or watch a good movie, it's just that maybe in that case I'll wear a mask. I don't know. But it's really your personal comfort, but definitely washing your hands makes a big difference and definitely like it was funny. I think you were... You may have been in the hallway yesterday, I don't remember, but I have a patient who I don't know has how many hundreds of birds, bird cages and stuff and he said can I do whatever he does with his birds and I said that's probably one that you can't because these bird type infections you can get and it's just not worth it. Gardeners, getting in the dirt, cleaning cat litter. All those things it's just a risk/benefit thing and it's just not worth it. It's not that you're going to get something for sure, it's just why would you mess with something like that? On the other hand, going to church, going to a movie, seeing your family that is worth it. You just have to balance out that risk.

**Q69:** Okay.

**Q70:** Relating to the same subject, I was told not to swim in our swimming pool, fungus.

**Dr. Eric Padron:** I'm not aware... I mean, as long as you take care of your pool and it's chlorinated and it's clean and stuff, I mean, chlorine is how you kill fungus. So, I don't know. I personally don't know of any increase risk from swimming in a private swimming pool. Maybe in a public swimming pool or a Jacuzzi.

**Sara Tinsley:** I think the hard part is there aren't studies that guide us. So, it's based on from one person to another the way they feel about...

**Q70:** It's basically have me living in a bubble.

**Dr. Eric Padron:** No. That I can tell you you don't have to do.

**Q70:** I'm not supposed to even touch fresh fruit and vegetables.

**Dr. Eric Padron:** Well, for instance, patients who are at Moffitt who have acute leukemia and are getting induction chemotherapy can have fruits and vegetables, but they're very well washed and so that's possible, but don't go to a buffet that is sort of...

**Sara Tinsley:** That sets out all day, lots of people touch the handles...

**Dr. Eric Padron:** Or a restaurant that is a little bit questionable. It's just about common sense really, but definitely living in a bubble is a wrong... If there is a wrong answer, it's living in a bubble because some of us here are dealing with a life threatening disease. I mean, that's fine,

but some of us are dealing with a life threatening disease here and I think it's important to recognize that that requires you more than ever to live your life as hard as it may be. So, my opinion would be and I can't put myself in your shoes, but my opinion would be you've got to live your life. You've got to do what you enjoy, but just temper it with some common sense and wash your hands and stuff.

**Sara Tinsley:** And I did write the section on Staying Well with MDS. Like the part about eating and how to... when you're neutropenic what can you eat, what should you avoid and do we have any evidence? Are there research studies that tell us how to eat and basically there's not research on that.

**Q71:** My daughter she's clinical neutropenia since ever and she always wears a mask when she's in close crowded places. Most in airplanes always and she's always carrying a sweater even though the weather is hot because you might experience change of weather when you go into a supermarket or whatever and a scarf because she's had five pneumonias and she's had several pyelonephritis. (inaudible 2:31:19) and now what she always has is because I take care of her always is just a herpes here that she's got it right now and sometimes infections in her nails and that's it. The other infections they are controlled.

**Sara Tinsley:** Wear a mask. Very good. Thank you.

**Q72:** Just on the white count question. Basically the follow the absolute neutrophil count. Does it make any difference as far as infection risk when there's shifts in the differential? Sometimes they like will do a manual dif and there are shifts that it's not normal. You'll see some of the cells are very... too high and others aren't low. Does that impact the infection risk with any significance?

**Sara Tinsley:** Are you talking like the type of cells in the differential aren't just neutrophils like sometimes the monocytes go up. I would say I would pay attention to your differential because you don't want to see a lot of atypical cells in there or blasts or a lot of lymphocytes or...

**Q73:** (inaudible 2:32:38) infection risk because if the ANC still usually doesn't look (inaudible).

**Sara Tinsley:** We normally look at the neutrophil count for infection risk, but we still do... I mean, that's one of the things you want to pay attention to is if there's blasts suddenly showing up because that could show that your disease is changing, but I focus on neutrophils and then look at the other ones just to see how they're changing.

**Dr. Eric Padron:** And that's exactly right and I also think that sometimes patients with MDS can have believe it or not a second problem in their bone marrow and there's a lot of well described co-occurrence diseases in the bone marrow of MDS patients. So sometimes when your lymphocytes are going up that could be important because it could be a sign of a second disease

or a reactive process. So, I would just echo Sarah's comments. Neutrophil's mostly for infection, but the rest of the differential is important to understand how your disease is behaving and that's why it's done so regularly.

**Sara Tinsley:** I mean, if it's just sporadic like you see changes then that's... I usually don't get concerned about it. If I see blasts then I want to make sure that I see if they go away and if it was a first time I ever saw blasts I would ask my doctor about it. Does this mean other things are changing?

No more questions? Oh, yeah.

**Q74:** My oncologist had cautioned me about getting a colonoscopy, which I am due because of a history of colon cancer. Is there any take on that?

**Dr. Eric Padron:** So, the theoretical risk is translocating bacteria which your gut is full of from the colon to the blood. So, I frankly am not aware of any data that says that risk is exceedingly high in MDS patients of that translocation event from occurring, but again everything has to be sort of taken with a risk/benefit analysis. If you have high risk MDS and you're dealing with what could be a life threatening disease and your last colonoscopy 10 years ago was completely clean then you have no reason to believe there's a problem. You don't see blood in your stool, you're not having any problems. I think it's totally reasonable to at this moment perhaps delay the colonoscopy so that you can focus on the treatment of your high risk MDS. Now if you have low risk MDS for what you're receiving no treatment things are completely fine, you're being watched and your ANC... your neutrophil count is just a bit low, I think you can make a strong argument to say I need to get colon cancer screening. This MDS is something I have, but it's not life threatening right now. It's something I'm going to be dealing with. So, I would then push to get your colonoscopy done. So, that's sort of how I would approach the problem.

**Sara Tinsley:** I know a lot of people ask me about dental cleanings. That comes up a lot, but that again is looking at the neutrophil count and seeing what's going on there and if your neutrophils are fine, you haven't had problems with infection you could get a cleaning, but if you're neutropenic then you might be more cautious like about if you can delay it if your neutrophils are down just because you got a treatment and they're going to come up then you want to time things when your counts are better.

**Q75:** (inaudible 2:36:38)

**Sara Tinsley:** Some people ask about dental cleanings which can be a problem when you're neutropenic for the same reasons like the colonoscopy. There's lots of bacteria in our mouth and if you have low neutrophils and they're digging around in there that could put you at risk for a bad infection.

**Q76:** What about low platelet counts? Same thing?

**Sara Tinsley:** Yes. Low platelet count and cleanings because then you're having the risk of bleeding from those and if you have low neutrophils. So, I would just be in really close communication with your team of healthcare providers.

**Q77:** What about eating out at restaurants?

**Dr. Eric Padron:** So again, I think eating out at restaurants is completely fine especially if you have cooked food. If you're going to a reputable restaurant, the nice restaurant, you're ordering a cooked meal and no one around is sick maybe you decide to go for a 4:30 dinner, I don't know, then, you know it's okay. There's no hard and fast rules. The only rule I guess I would say is don't live in the bubble. That's the only rule. Other than that... Common sense.

**Q77:** But you don't know where the server's hands have been prior to serving you.

**Dr. Eric Padron:** Oh, yeah. You don't know where the server's hands have been. You don't know where the cashier's hands have been. You don't know where your neighbor's hands have been. You really are at an increased risk, but if you wash your hands and you use common sense you can lower that risk and it's just a balance. It really is. I think the bottom line is to say as I was mentioning earlier a typical MDS patient is not at an extraordinary risk of getting infection to the point where someone shakes your hand they will get it. It's not like that. It's not that you're 100 percent of the time going to get someone's infection. It's just you're at a much higher risk than someone who doesn't have MDS and has a competent immune system. That being said you just have to use, again, common sense and wash your hands, wear a mask where you feel appropriate, but you can go out and eat dinner, you can interact with people. You just may not want to interact with sick people.

**Sara Tinsley:** And monitoring your temperature and if you're getting new symptoms you would want to report those.

**Q78:** I have a question concerning the Vidaza. I saw on the chart at first counts will go down and then you said generally they'll go back up. Well, I had very high platelet counts. They range anywhere from 500 to 800,000. So, the Vidaza would bring that down?

**Sara Tinsley:** Yes. It would bring your platelet count down.

**Q78:** And then when it goes back up is it going to go back up to 500-800,000 or...?

**Sara Tinsley:** Normally, in the first two cycles of treatment it'll go down lower because everything is a little lower in the beginning, but then sometimes you can see it either go back to the way it was or even overshoot, go a little higher, but that's normally a sign that you're



responding if that's happening around your third or fourth cycle. If your blood counts are getting higher and better, but if you had a thrombocytosis associated with your MDS where your platelets are high...

**Q78:** Yeah. I do. RARS...

**Sara Tinsley:** RARST?

**Dr. Eric Padron:** Is that what you have? I was just about to say that because other than the 5Q-syndrome, an MDS patient will not have a platelet count as high as 800,000 unless you have one of the overlap syndromes like CMML, RARST, atypical CML. So if you have RARST that absolutely makes sense.

**Q79:** Everything seems to be related pretty much to the five chromosome. I have a 20Q deletion. Is that pretty rare or...?

**Dr. Eric Padron:** So, it's not rare in the grand scheme of things. It's a deletion of 20Q is one of the more common chromosomal abnormalities across myeloid malignancies. So, it's usually associated with a loss of a gene called RUNX1 and it has been associated that people with deletion of 20Q have lower platelet counts than people that don't have 20Q and it's also usually thought to be one of the sort of more benign lesions so that we have patients with isolated 20Q who do fairly well with... That's the one category that's common where you have low risk disease, you have 20Q, but you have a low platelet count. That's sort of the picture that is typical of a 20Q patient. I'm not sure if that's the case for you, but that's sort of what we think about when we think about 20Q.

**Q79:** Okay. Thank you.

**Q80:** You talked before you had mentioned 5Q, 7, 20. Are there some sort of set of chromosomes that are what you'd call a subset like you talked about 5, 7? Okay, now he mentioned 20. Are there others that are like more common?

**Dr. Eric Padron:** So, there are... so first of all only about 30 or 40 percent of patients with MDS will have a chromosomal abnormality. The rest will be normal chromosomes. Second, remember these chromosomes... just to clarify these chromosomes are on every cell of your body. They're just in the cancer cells. So if I were to biopsy your skin or your hair or your liver and look at the chromosomes, they would be normal and third there are an array of chromosomes which have a variety of implications. So some of the chromosomes are favorable like isolated deletion of 5Q, 20Q, the loss of Y in a male. Those are all favorable. There are some that by themselves are unfavorable. Mostly abnormalities of chromosome 7 and losses of 17P which is where P53 lies and then there is essentially just like the question was asked about number of mutations. The same thing is true for chromosome abnormalities. The more chromosomes

abnormalities you have the more complex and aggressive we think the disease will behave and especially true in monosomy. So if you have, say, monosomies of 5, 7, 13 the more monosomies you have we think that's going to be a more aggressive behaving disease. There are also some diagnostic implications. So, there are some chromosome abnormalities that are disease defining. So, I'll give you an example. There's chromosome abnormalities of 16 and there's a fusion between 8 and 21. Now if you have an inversion 16 that's defining of acute leukemia even if you don't have increased blasts, but on the other hand it's also suggestive of a favorable acute leukemia. So, there are some chromosome patterns that are disease defining, some that are seen across myeloid neoplasms, some that are prognostic, some that are not and so there's a whole mishmash of things that people like me have to worry about, but I think for your perspective, some have clinical relevance, some don't. You just have to look at the individual pattern.

**Q80:** Yeah. That's what I have is 16.

**Dr. Eric Padron:** Inversion 16?

**Q80:** Short?

**Dr. Eric Padron:** Yeah. So, that's an AML defining lesion. Yeah.

**Q81:** What was A21 indicative of?

**Dr. Eric Padron:** AML defining.

**Q81:** A21?

**Dr. Eric Padron:** That's right.

**Q82:** I think you mentioned a mutation that was favorable, SB something. What's the prognosis of that?

**Dr. Eric Padron:** Well, SF3B1 mutations are seen in about 20 to 30 percent of all MDS and they're seen at about 80 percent of patients who have MDS and the ring sideroblasts that we talked about and the prognosis relative to other MDSs is favorable. Almost all of those patients have low risk disease and in fact if you have SF3B1 mutation and nothing else they're taken out of any genetic analysis as their own sort of outlying group so much so that the last World Health Organization meeting on MDS there was some debate although it didn't pass through of just making this an entity, this SF3B1 mutant MDS because it has its own distinct behavior. So, I don't know if that answers your question. I don't know that it's relevant to give an exact number and I don't think I have it memorized the exact median survival for isolated SF3B1 mutants, but in general that's what you think of.

We have a question over here?

**Sara Tinsley:** Does somebody else have a question?

**Q83:** Can the disease jump back and forth between MDS and AML? The cutoff is at generally is what, 20?

**Dr. Eric Padron:** Yeah.

**Q83:** Then if it goes over 20 does it ever come back?

**Dr. Eric Padron:** Practically speaking, yes. Technically speaking, no. So practically, yes. You see patients have, say, 30 percent blasts are put on Vidaza and they get a response, they have partial response and they go to 10 percent and they can stay there for a while. So practically, yeah, you see that, but technically once you have AML you're AML. So, let's say you have AML. We give you the high dose hospitalized chemotherapy for a month that people with AML get and then you do okay and then a few months later we see six percent blasts. By definition you have relapsed AML, but technically there are some people that stay there for a while. So, it's a question of the practical interpretation versus the technical interpretation.

**Q84:** At what point then do they consider a transplant?

**Dr. Eric Padron:** So, I guess the broader question that I can start talking about is what happens if your disease transformed to AML, the so called secondary AML. So, I'll just tell you a couple things about secondary AML and then what the general practice was and is now. So, secondary AML the definition of it is you had antecedent hematologic malignancy whether it's MDS or something else and then develop AML as measured by a blast percentage of 20 percent or more in your blood or your bone marrow. So, sometimes we see patients that come with AML and hadn't been to the doctor in five years and aren't really sure whether their counts were low back then and so it's conceivable that they may have had MDS in the past and just didn't know it until they transformed and there's recent studies that show that if we look at the pattern of your mutations at the time when you have AML we can predict whether you had MDS in the past, the now so called secondary-like AML. So if you secondary or secondary-like AML what happens next? So, the first question is how strong are you physically? So, are you the person that has trouble getting out of bed, can't take a shower because you're so tired, can't walk around the block? Are you the person that's otherwise healthy and if this problem was gone you'd be in great shape. If you're the latter then usually what we do is the induction chemotherapy which is either five or seven days straight of chemotherapy in the hospital and a full hospital stay of about three to four weeks. In that instance depending on what chemotherapy they use, about half of people can go into a complete remission meaning we don't see it anymore. After the complete remission, there's a very important question asked is should you go to a transplant now or should you be given chemotherapy and wait and in some people if you give chemotherapy and wait it

doesn't come back and in other people if you give chemotherapy and wait it comes back and at that point anybody who has it as a second relapse or the first relapse really should go for a transplant. So, how do you decide if at the first time you should get a transplant? It's really your chromosome pattern and your genetics. It used to be the case that patients who had MDS and transformed to AML were universally taken to transplant because it was thought that sort of pound for pound it was the most aggressive type of acute myeloid leukemia. So if you get it into remission, you got to take them to transplant, but what we know now is it really isn't the fact that you had MDS in the past that made it aggressive. It's just the fact that those that transformed from AML typically has the aggressive genetics that then dictate the behavior of AML. So, there's actually some patients who have secondary AML, but have good genetics and in those people now we probably wait and it's really only the genetics, the chromosomes that dictate to us whether your disease will be aggressive or not and whether we think a transplant is warranted at the time.

**Q84:** Thank you.

**Dr. Eric Padron:** I don't know if Sue's around, but I know the agenda goes till, is it two o'clock and it's now... So, I guess there's two options. We can either answer more questions or call it a day. I think we maybe we should ask Sue what... or ask you guys what you want to do.

**Q85:** When was the iron...?

**Dr. Eric Padron:** That's at 2:30 and I mean if it's up to me we can push it up as well. If you want to just start doing that. Well, what we'll do is we'll take a 15 – 20 minute break or actually why don't we start at 2:00. Want to do that? Okay. We'll start at 2:00.