

Speakers:

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**Virginia Klimek, MD:** With that we'll get started.

So, I think what I've found when I've spoken to these groups is that people come to these forums may have been diagnosed a month ago or a month before the forum or there are people who may have had this diagnosis for many years. So, I find that there's a range of understanding and knowledge and experience with this condition. So, I usually like to start off by talking a little bit about some basics – what is MDS and then start working through some of the other questions that you may have about treatment.

So, MDS stands for Myelodysplastic Syndrome. It's a complicated name, but if you break it down myelo is just a fancy word for bone marrow, dysplastic means that the cells are abnormal and then syndrome, it's called a syndrome because in addition to the bone marrow the way the bone marrow looks, you have to look at a lot of other blood tests and bone marrow tests and a combination of these findings is what we call a syndrome. So, it's a disease of the bone marrow. If anybody's gone online and looked this up what you'll find is that we really do consider Myelodysplastic Syndrome as not only a disease of the bone marrow but a cancer of the bone marrow. It's considered an abnormal growth of the cells in the bone marrow which is really what cancers are. If you think about other cancers like breast cancer or colon cancer you have an abnormal growth or tumor. In MDS you don't have a tumor growing in your bone marrow. You just have a lot of abnormal cells growing throughout the bone marrow liquid.

The overall... the biggest problem in MDS is that with these abnormal cells growing in your bone marrow, your bone marrow can't function normally and you end up with low blood counts and for about a third of people it can develop into acute leukemia. So, bone marrow is the material inside of your bone and I always talk to my patients about the concept that your bone marrow space is basically a blood cell factory. That's where all your blood cells are made and when the production process is finished, if you will, they leave the bone marrow and they go out into the blood stream and that's where we test your blood count. So, your blood cells that all end up in the blood stream actually start inside your bone and in adults most of the bone marrow function and the blood cell production are in like the hips bones which is why we go in that area to do the bone marrow test that we take. Also like the long bones of the body, the thighs and the upper arms and also in the spine.

This is a picture of your leg bone, the upper leg bone, and you can see that... So, inside the bone is the bone marrows and that's where you produce all the three main types of cells that you need. These are the red blood cells and there's many different types of white blood cells that make up

your immune system and then you have cells that are called platelets and the platelets are cells that help promote blood clotting formation.

So, red blood cells. Red blood cells are basically bags of hemoglobin. Hemoglobin, the job of hemoglobin is to carry oxygen to your brain, to your heart, to your lungs to your muscles and that hemoglobin molecule carries oxygen to all those cells. Neutrophils are one of the white blood cells. Those are your main infection fighting cells. That's why your doctor talks to you all the time about the importance of looking at your neutrophil count because of the risk of infection and as I mentioned before you platelets, the job of the platelets is to prevent and stop bleeding.

So, when is MDS suspected? So, I'm going to bet that if I go to every table and I talk to whoever's here that has MDS that you're going to tell me maybe in this room there's at least five different ways that people were diagnosed with MDS. One is just that they went to the doctor for their annual checkup and they were a little anemic and they said you know we better watch this and then over time the hemoglobin went down and then your doctor referred to a hematologist and you had your bone marrow and you were diagnosed or you were fatigued. You went to your doctor you were fatigued and that's when they picked up the fact that you were anemic or you started having bleeding problems and that's when they found out your platelets were low or you might be just going in for like a pre-surgical checkup before your knee surgery and they found out that your blood counts were abnormal. Every once in a while people have x-rays or MRIs done of the bone marrow and the bone marrow looks abnormal and that's how it's diagnosed. MDS is more likely as we get older in your 60s, 70s and 80s. So, if somebody comes to the doctor and they have anemia that just started when they're about 65 or 70 years old that increases the odds that you might end up being diagnosed with this condition. It may also be more likely if you've had another cancer and you've had chemotherapy or radiation because that chemotherapy or radiation can cause damage to the bone marrow and cause something called therapy related MDS.

The tricky thing about diagnosis MDS is that some of the symptoms from MDS are very common and they're seen in a lot of other conditions. So, fatigue, shortness of breath from anemia, weakness from anemia, infections from low blood counts or bleeding or bruising tendency, I can think of 10 medical conditions that can cause all of those things and so MDS can mimic a lot of other medical problems. So, sometimes the diagnosis might be delayed because the doctor thinks wow there must be something wrong with your heart because you're having a hard time breathing or you can't walk as long as you can. You can't walk up those stairs. Or if you have a bleeding or bruising tendency if you've had a stent in your heart and you're on a medicine called Plavix or aspirin you might be bleeding or bruising more easily. So, there are other conditions that can cause the same problems and can actually mask or exacerbate the MDS condition because you have two factors that are affecting your blood count.

So, the way we diagnose MDS is first to take a really detailed medical history and we have to think about all those other medical problems that can cause those symptoms and that can cause

low blood counts. Medications are very important part of this assessment because a lot of medications can lower the blood counts. The complete blood count or the hemoglobin, the white count and the platelet levels and importantly looking at the actually how the cells look under the microscope because you can get clues by actually looking at how the cells look under the microscope. Your doctor has to do a lot of blood tests to rule out a lot of those other medical causes of low blood counts, but if all of those other blood tests fail to show a reason for those low blood counts that's when you end up getting the bone marrow exam. Does all this sound like a familiar path for everybody? Yeah.

And I'm sure this looks familiar. This is a necessary evil for making a diagnosis of MDS. You really can't make a diagnosis. You can do blood tests that give you a hint that somebody has MDS, but you really need to do this bone marrow test and do a variety of tests on the bone marrow to look for things like dysplasia. Those are the abnormal appearance that you can see when you look under a microscope. Everybody in this room if you've done any reading you understand the importance of blast counts. Now, everybody in this room whether you have MDS or not has blasts in your bone marrow, but the thing we worry about in MDS is that the blasts can go up and increase your risk of developing leukemia. We look at the genetics or cytogenetics. We look at iron stains. We look at something called sideroblast stains. I met a gentleman before the talk today who told me he had RARS and so he and I'm sure many people in this room either have this or are aware of this important finding in terms of how it can help us establish a diagnosis. We also do something called immunophenotyping. This is a complicated word for a test that we do to look for proteins on the surface of your cells and your bone marrow that tell us if your... if the cells in the bone marrow are developing abnormally. It's sort of an indication of this dysplasia problem. So, if the cells are developing abnormally they have abnormal proteins on their surface.

So, how do we decide that somebody has MDS? It's important to understand that there's no one single test that tells you whether somebody has MDS or not. As I mentioned before, first you need to eliminate a lot of other causes of low blood counts and then you also need to see these typical findings that we see in the bone marrow, the dysplasia, perhaps increase in blasts, these chromosome abnormalities although that's only seen in about 50 percent of people. Nowadays we're also using genetic mutations to try to see if the evidence is leaning more towards somebody having MDS or not and this hypercellularity feature means that when you look inside the bone marrow... remember that picture of that bone I showed you in the marrow space, for a given person anywhere from half to three-quarters of the bone marrow should be taken up by fat. It's normal to have fat inside your bone marrow, but most people with MDS have a marrow that's just filled up almost completely with blood cells, but the problem is is that it's inefficient. Your bone marrow's not producing enough cells even though there's a lot of activity the output is really poor and when I think about this I think about and everybody... most of the people know the show "I Love Lucy," the old show "I Love Lucy" and the chocolate factory. So, it's just like there's a lot of activity and everything, but the output is really bad. So, when we're trying to decide if somebody has MDS sometimes we'll do all of these tests and we're not sure.

Is there anybody in this room who's ever been told initially well, we're not sure you have MDS? We have to watch and wait. Yeah. I see a couple nodding heads and hands. Yeah. That's hard because you just want the answer and you want to move on and treat it and figure out how we're going to treat it, but this watch and wait approach is sometimes we have to take and when we do that we just follow blood counts and then, of course, our favorite thing to do we have to repeat bone marrow tests. We may have to do two or three bone marrow tests to just confirm that somebody has it, but it's important and the reason that it's important is because as many of you here know once an MDS diagnosis is established we know it's a serious disease. Right? We know it's difficult to treat. It's a serious disease. We're making big decisions about chemotherapy, no chemotherapy, maybe stem cell transplant. So, we want to be sure and if it means watching and waiting for a while or repeating a bone marrow it's important to do that.

I want to just go back a little bit to some of the other causes of low blood counts because these are frequent questions that my patients ask me, but these are the types of things that we try to rule out if you will when somebody comes in with low counts. You can have low vitamin levels, you can have low iron levels, many drugs including other ones not even listed here can produce low blood counts, infections, other cancers can do this, even other medical diseases like kidney disease, arthritis, lupus, other bone marrow disorders we have to distinguish from including this list of complicated diseases like aplastic anemia, paroxysmal nocturnal hemoglobinuria. There's going to be a quiz. Hairy cell leukemia and myeloproliferative disorders. There's also inborn genetic disorders that we're not going to really talk about much today because this is really something that is diagnosed usually at a younger age and it's usually more of a pediatric patient population issue.

Now, is anybody here familiar with ven diagrams? So, ven diagrams what we use these for is to say okay where is there overlap between concepts or two ideas. This is what your hematologist is thinking about when they're looking at you when you walk in the door with low blood counts because here's MDS in the middle, but look at all these things that sort of intersect with this yellow circle. These are all the things that can possibly... we can possibly find in your marrow or come out of the workup from looking at the combination of your blood and your bone marrow. So, there's many things that can cause low blood counts. So, again, this is a complicated diagram, but just to give you a sense that there's a lot of things that we have to think about and rule out before we can establish a diagnosis of MDS.

So, just to summarize, MDS is an abnormal bone marrow condition. It's a bone marrow cancer that results in abnormal maturation and development of blood cells, low blood counts because of underproduction of blood cells. For about a third of people potential that it could change into something called acute leukemia and it's very heterogeneous. Like I said before about going to different tables and talking to different people there are so many different variations of this disease in terms of the bone marrow findings, the fact that somebody can come to the doctor with just anemia or low platelets or low white counts or all three and everybody... if you meet other

people here in the room and you start comparing notes you'll find that a lot of people have a story that's different than yours. So, it's very heterogeneous.

So, I think what I wanted to do now at this point is just to take a break and if there's some questions and I got a list of questions that some people submitted and I'm happy to take those questions from the people who gave me these at any time during the meeting, but we may cover these as well just as other people ask questions. So, does anybody have any questions at this point?

**Q1:** (inaudible 15:22 – 15:33)

**Virginia Klimek, MD:** So, there are some antibiotics that can do this. One of the ones that we worry about and we try to avoid in people who have Myelodysplastic Syndrome is something called bactrim. For example, there are medicines that people take, antacids if you will. I don't know if you want to jump in. Amber, if you want to jump in. She can help answer that.

**Amber King:** (inaudible) there's a lot of (inaudible) bone marrow. So, big ones are a group of things called...

**Virginia Klimek, MD:** I don't think everybody can see you.

**Amber King:** This one called (inaudible 16:14) and so overall (inaudible).

**Virginia Klimek, MD:** The other thing I would add to that is that if you read studies that report on the incidents of low blood counts with a given drug, usually those studies I would almost guarantee you that those studies were done in either people who were healthy and didn't have a problem with their bone marrow or they had other conditions that didn't affect the blood counts. So, we view just about any drug as something that could potentially lower the blood count in the setting of somebody having a bone marrow disorder like MDS because if you have MDS, your bone marrow reserves, if you will, your blood productions reserves are not normal. So, even if a drug is not associated like... even if a drug doesn't have like a reported incidents of low platelets...

**Q2:** (inaudible 17:34)

**Virginia Klimek, MD:** Yes. So, what we find... we have to do a lot of detective work, but if somebody comes in the room and comes to see me and they said you know, I got started on this blood pressure medication about a year ago and oh yeah that's about when I started seeing the change in my blood counts. We just sort of try to correlate things and then sometimes we'll experiment. We'll say okay let's stop that medicine or switch it to something and then we'll talk to your cardiologist before we do that. So, sometimes we'll try to do that because even medicines



that aren't typically associated with low blood counts can affect the blood counts in people with MDS.

**Q3:** (inaudible 18:12 – 18:26)

**Virginia Klimek, MD:** Yeah. Yeah, yeah, yeah. So, it's... so even somebody who's having blood work done regularly if they're going for their annual checkup if we go back and then they ultimately get... eventually get diagnosed with MDS, I find that if we go back let's say if we go back a few years we can see that maybe there was a hint that even if it was still in the normal range that it may have been coming down a little slowly and so we really do think that when MDS is diagnosed it's not diagnosed on the day... it's diagnosed on the day that we do the bone marrow, but the reality is it started either weeks, months or sometimes even years before and we can't say definitely when it started. The best we can do is go back in time and find the best evidence that we can meaning the blood counts to see when they started dropping and kind of guess when it started. Yeah.

**Q4:** Can I ask a question? I was diagnosed about eight years ago. The first bone marrow showed a presence of a low grade lymphoma and then we went into the wait and watch segment of my life and then eventually a second bone marrow started to show the presence of MDS and since then I've had two or three or four bone marrows and the last one was about a year ago and the presence of the lymphoma seems to have almost faded to a great degree and the MDS is basically what we've been treating, but the question I have is I was under the impression that because I had the presence of that low grade lymphoma, I could not participate in the clinical trial for MDS. Is that true?

**Virginia Klimek, MD:** So, remember the slides I showed you about the problems that we have in MDS. It's the low blood counts and it's due to the fact that you have these abnormal bone marrow cells that can't produce enough blood cells. So, what do we want to fix in MDS? Well, let me take a step back. So, the other problem you could have is that the blast counts can be elevated and maybe you don't have that problem, but some people in this room do. So, what we're trying to fix when we're trying to fix and find new treatments for MDS is we're trying to find ways to improve the blood counts and lower the blast counts. So, if you have another disease... if you have another disease process or cancer in the bone marrow that could be affecting your blood counts it interferes with our ability to interpret the maximal benefit of the drug, that new drug, the experimental drug in that clinical study. So, if you have another condition that can affect bone marrow function you're generally not allowed to go into clinical trials where they're testing the effect of that drug on your blood counts because they're worried that that lymphoma's going to interfere your bone marrow's ability to respond maximally to the drug. I think that that's a... I understand why they do that. I know that I do my best when I run and design clinical studies to try to include people because I feel if you have a stable cancer like many of these low grade lymphomas can be stable for years. If they're stable for months to a year or so it's like a known entity and you can still look at that person's bone marrow function

and see if it improves during the time on the study, but unfortunately many clinical trials that are... particularly ones that are run by pharmaceutical companies are very... they're very strict because they've got on the line. They're trying to show that this drug work. It's just... so, you're correct. You're correct.

**Q4:** Okay. Thank you.

**Q5:** You said that approximately a third of people with MDS will get (inaudible 22:18)

**Virginia Klimek, MD:** All comers. Yeah. If they're all comers. Yeah.

**Q5:** (inaudible 22:24) my oncologist and someone (inaudible) that there's percentages of (inaudible) 67 percent, 89 percent (inaudible) I know there's not a specific percentage, but it's a very wide range and I like your numbers.

**Virginia Klimek, MD:** But... Yeah. But if you start to parse it out... if you really start to drill down and you look at specific groups, of subgroups of people and particularly looking at the genetics so if... and have you ever heard of something called the IPSS score? Many people...

**Q5:** I've (inaudible 23:14) about it.

**Virginia Klimek, MD:** Yeah and there's more information in these really great books that they're giving out today about this International Prognostic Scoring System. It's a way that we can... it's a method that we can use to estimate how long people can live with their disease without treatment and what the likelihood is of developing leukemia. We know that if you have certain types of genetics... Genetics are becoming increasingly important not only in this disease but in cancers as we learn more about it, but if you have certain genetic abnormalities or multiple genetic abnormalities and maybe even a particular mutation like something called a P53 or TP53 mutation. We know that during your lifetime with this disease you're virtually guaranteed to get leukemia versus somebody maybe with RARS subtype, classic RARS subtype. Their chances are probably less than 10 percent. Do you know what I'm saying? So, it depends on the genetics and the subtype.

**Q6:** (inaudible 24:12) every time they do a bone marrow or should we be asking for that?

**Virginia Klimek, MD:** So, at the time of diagnosis the standard tests that we do include just looking at the cells to see how they look, the genetics test, specifically it's called cytogenetics where we look at the chromosomes and then plus or minus these mutation tests which are a little newer, but they're sort of a newer way that we're using to study and learn about these diseases. This score is based on those genetics, the blast count and the blood counts and you... at diagnosis you should have all of that... all of that should be done. Generally on follow up bone marrows, that should all be done and if... (Attendee), do we have... on the MDS Foundation

site, is there a link for your calculator? Your IPSS-R calculator? So, maybe... and maybe you can help me to find so I can direct them where to find it, but there's actually an online calculator. If you go online you can actually go online and you can calculate your own score. But yes, you should ask what your score is. It's most important to know that score at the time of diagnosis though. Most of these scoring systems are useful at the time of diagnosis. If you do it like three or four years into your treatment I mean, they're really not designed to use that way. They're best used and they give the most information when you use them using the information from the time of diagnosis.

**Q6:** And would that (inaudible 25:54) with the percentage of blast (inaudible) one percent and five percent and ten percent. (inaudible) Does that have anything to do (inaudible)

**Virginia Klimek, MD:** Absolutely. Yeah. It's one of the things that are included in the prognostic score that we were just talking about, this IPSS-R. Probably the most important thing though, the most... the thing that really predicts your score the most is your genetics though, the cytogenetics.

**Q7:** Just (inaudible 26:28) as you go through life and your bone marrow's (inaudible) immature (inaudible) and sometimes you get a bad (inaudible) but you go through life are you always getting more and more mutations?

**Virginia Klimek, MD:** That's a really good question. So, what happens is that... so, let's just talk about the genetics first. Generally, the genetics that you start off with in your bone marrow... again, this is not genetics you were born with. This is not the DNA you were born with. These are the genetics or the cytogenetics in the cells in your bone marrow that are part of your MDS disease. Generally the ones that you start off with if you're not receiving therapy they stay there, but yes you can accumulate additional ones and generally when that happens that's when we see changes in the blood counts, changes for the worst. So, the disease can evolve or progress genetically and that's something that we can see along with changes in the blood count.

**Q8:** A statement you made before about the genetics and they do with bone marrow. I'm in a clinical trial at Weill Cornell.

**Virginia Klimek, MD:** Where?

**Q8:** Weill Cornell and in that when they do my bone marrow which is every third cycle on the (inaudible 28:19) plus a drug from (inaudible) and they do the genetic testing every other biopsy. Does that make sense or should they be doing the genetics for each of biopsies?

**Virginia Klimek, MD:** What they're looking for is they're looking to get a sense of how long this drug is taking to work unlike what we were just talking about before how the genetic changes can accumulate over time if you're not on treatment. What they're looking for is to see



if the genetic... the chromosome abnormalities if they decreased in number or go away over time. Generally, the treatments... is it a three or a four week treatment cycle?

**Q8:** It's generally four, but it's gone out as long as five based on my counts.

**Virginia Klimek, MD:** I think there's no standard... So, what we sometimes do in clinical trials is we'll check for the genetic changes, the blasts and everything once a month until we sort of get past the point where we think people are likely to show a response and then we'll space things out because we don't want to have to do bone marrows on you every month, right, and it's... and those tests can be expensive. So, it sounds like they're trying to find sort of a happy medium in terms of the frequency and what they're going to learn from that.

**Q8:** Thank you.

**Virginia Klimek, MD:** You're welcome.

**Q9:** These are the FISH studies. Is that (inaudible 29:52).

**Virginia Klimek, MD:** That's one of them. Yeah, yeah, yeah. So, a karyotype and I'm sorry this... and I think the books from the MDS Foundation have nice glossaries in them, too, and that 100 questions book is really good if you have focused questions like this. Karyotype looks at your chromosomes and that's just sort of like a global look at all of your chromosomes, your regular chromosomes plus your sex chromosome, but FISH stands for fluorescent in situ hybridization. So, what they do there's a list of like usual suspects of genetic changes that we see and what the FISH does is it gives us like a fluorescent probe that goes searching for those usual suspects and so you can pick up ones that we know exist in MDS and the common ones. The karyotype just gives more of a global survey. So you can pick up some of these rarer ones where we don't have FISH probes, but they're complementary the karyotype in the FISH.

**Q10:** (inaudible 30:56 – 31:22)

**Virginia Klimek, MD:** TP53.

**Q10:** (inaudible 31:24 – 31:47)

**Virginia Klimek, MD:** So, the deletion 5Q that can be picked up by FISH that can usually be picked up in the blood as well as bone marrow. Was this in the blood?

**Q10:** (inaudible 3:57)

**Virginia Klimek, MD:** It's blood. So, yes. The bone marrow will... so as I mentioned before the FISH can only pick up certain ones that are on the usual suspects list, certain abnormalities, but

there's many more abnormalities that you can pick up by doing the karyotype. So, when you do the bone marrow test we can do the karyotype. The karyotype just doesn't work very well on the blood because the cells have to grow in culture. Technically, it's a little complicated to explain, but we can't usually do a karyotype on the blood, but on the bone marrow they'll be able to do more of global survey of the genetics as well as look at the cells to see if they look abnormal and also count the blasts.

I saw some other hands.

**Q11:** I have a question related to unexplained symptoms. I take no drugs whatsoever. I'm physically very active and eat a very healthful diet. I've been experiencing over quite a period absolutely no appetite whatsoever. Without any explanation different random times I'd become breathless. I also become fatigued. It lasts a very short time. Doctors ruled out almost everything. I'm just trying to find out what that might be. Could it be related to MDS?

**Virginia Klimek, MD:** So, when you have fatigue or breathlessness from MDS, it doesn't tend to just come and go transiently. It tends to be and I'm sure in this room can attest to that. It tends to be something that just stays with you...

**Q11:** No.

**Virginia Klimek, MD:** ... and over time as your hemoglobin goes lower it gets worse. So, to have something come and go it makes me think that there might be some other medical problem in play which is not to say that if you're anemic from MDS...

**Q11:** Yeah. Very mild anemia.

**Virginia Klimek, MD:** If you're anemic from MDS or any other medical condition it can bring out the breathlessness or the fatigue that's due to like an underlying heart problem. You know what I'm saying? So, the two things together can make the symptoms worse. So, it may not be the main thing, the anemia for whatever reason you have anemia, but it could be other things that are affecting your health.

**Q11:** Well, monocytosis is present. Platelets are kind of low. They've gone down as low as 37 and was put on a four day course of Prednisone, low dose which brought it back up a bit, but it's a changing (inaudible 34:25)

**Virginia Klimek, MD:** See, but those types of symptoms would require that we rule out certain... just to give you some examples and not to go into... because I can't pretend I know everything that's going on just what you're telling me, but I can right off the bat I can think of a couple infections that can cause those symptoms or other... unfortunately other malignancies, too. So, there's other things that can cause all of those symptoms that you're talking about not

necessarily the transient changes in your breathing. So, this is why this disease can be so difficult to diagnose because a lot of the symptoms that you have with MDS are also seen in other medical conditions and other medical conditions can affect the way the anemia, for example, or the low platelet count affects the way you feel. It's really complicated.

**Q11:** At this point cardio has been ruled out.

**Virginia Klimek, MD:** Pardon me?

**Q11:** At this point cardio has been ruled out. Still don't know what it is. When I exercise I feel great, never out of breath and then for no known reason that breathlessness and the fatigue are separate, separate incidents, but the loss of appetite is constant.

**Virginia Klimek, MD:** I can't say I know what's happening.

**Q11:** I just thought I'd ask.

**Virginia Klimek, MD:** No, no, no, but I think just to get back to my initial point when the main problem is low blood counts from the MDS, it's usually... it doesn't fluctuate day to day or week to week. It's usually just there and it's just persistent.

Yes?

**Q12:** I have a (inaudible 35:53) I have fatigue (inaudible) I'm on (inaudible) the last three months and everything... my blood counts are just staying like they are. They're not really going up or down, stationary. That (inaudible) it will eventually it will work won't it?

**Virginia Klimek, MD:** So, there's a couple different names for what he's referring to. One is Vidaza, also 5-Azacitidine is the other name for it and we're going to talk a little bit more about the specifics of what to expect. Kelly's going to do a nice presentation on that, but the quick answer is that it can take four to six cycles to start seeing that drug work. So, you got to kind of stick with it and kind of invest that time.

Right? You'll talk about it.

**Q12:** Thank you.

**Virginia Klimek, MD:** You're welcome.

**Q13:** (inaudible 36:47) IPSS score is the more likely you are to (inaudible). How does that impact your (inaudible)?

**Virginia Klimek, MD:** You mean at the time of diagnosis if it's close?

**Q13:** (inaudible 37:07 – 37:17)

**Virginia Klimek, MD:** It would mean just a more aggressive treatment type meaning we would consider transplant right away or at least chemotherapy right away and the monitoring is more intense. Instead of saying I'll come back and check your counts every three months we may be checking them every week. You know what I'm saying?

**Q13:** (inaudible 37:37 – 37:45)

**Virginia Klimek, MD:** Yeah. Absolutely. Yeah. Yeah. So, if the MDS progresses to leukemia you can still have a stem cell transplant, but generally you need to get that leukemia under control and get it back sort of into a MDS phase before you go onto transplant because the transplant is likely to work better that way.

**Q13:** So, (inaudible 38:03 – 38:08)

**Virginia Klimek, MD:** Yes. Yes. But that involves pretty intense chemotherapy.

**Q14:** (inaudible 38:14) on your comments earlier. The effects of MDS on the body. Is (inaudible 38:19 – 38:34)

**Virginia Klimek, MD:** Right. So, the answer to this question explains why we're always telling you need to come back every two weeks or every month or every three months for blood counts. So, there's no way to say that let's say that I know it's going to take a year from now for your counts to change significantly. That would require that we step in and give you treatment. It's generally linear, but we know that sometimes there can be abrupt changes and that's what we're looking for when we're monitoring people over time. So, I would say most people the changes occur linearly, but every once in a while we get surprised, hopefully not surprised because we're monitoring you regularly, but there can be sort of a sudden downturn in the counts or an upswing in the blasts.

How are we doing?

**Q15:** (inaudible 39:21 – 39:33)

**Virginia Klimek, MD:** Yes, with treatment. Yes, with treatment with treatment. No, no.

I was just looking we have some more material and actually some of the material we're going to go through in the next segment or two is going to address some of the questions that have been

coming up. So, hold some questions and don't forget that when you talk to press the green button or the red button? The red button.

So, I never heard of MDS until I was told that I had it because this is a common thing that people tell me when they come in to see me. MDS is not a common cancer. So, if you think about the cancers that you know that affect your family members and friends it's usually breast cancer or it's commonly breast cancer, colon cancer, maybe prostate or lung cancer. MDS is considered a rare disease. However, we know that as we get older as we get into the 60s, 70s and 80s, the incidents goes up and just for comparison like a rough estimate of incidents in the United States, it's the 10 to 20,000 cases per year, but think about breast cancer. It's probably closer to 250,000 new cases a year. So, this is a rare condition.

Nobody's asked me this yet, but this is a common question that I get when I see patients. How did I get this? Was it something I did? Was it because I colored my hair? Was it because I smoked? I worked in a factory for years before I retired. Was I born with this? These are all very common and very good questions, but the reality is that for most people there's probably more than one factor in play. So, I already touched briefly on the fact that if you have chemotherapy or radiation for a prior cancer, it can cause damage to the bone marrow and cause therapy related MDS. Mostly in younger people under the age of 50, but if you have inherited defects in your DNA that you were born with you're more prone to cancers as well as MDS.

**Q16:** (inaudible 41:47 – 41:56)

**Virginia Klimek, MD:** Vast, vast majority of people it is not an inherited disease. This is mostly in younger people and it's very rare. It's very rare.

Benzene and other solvents like benzene are probably the best established connection between some sort of a chemical exposure and developing MDS as well as nonmedical radiation. Let's say if you had a radiation from a... I don't know. I had a patient who used to... when he was young... I guess years ago they used to size people's shoes by doing an x-ray. Right? So, I had a patient who was the son of a man who owned a shoe store and they used to play with it all day. And then in recent years this is really become... in recent years we're developing a better understanding about why MDS develops in people in their 60s, 70s and 80s. We're finding that there are age related changes in your bone marrow that basically set you up. They set us up to develop this and we have a ways to go to figure this out, but we're finding out that some of these mutations even P53 mutations are found in people way before they had MDS or way before they were treated for lymphoma and then after the treatment for the lymphoma they developed MDS with that same P53 mutation. So, we're finding out that easily 15 percent of people over the age of 70 are walking around with mutations with normal blood counts and what we're trying to understand now is how these mutations set us up for developing these bone marrow diseases down the road. So, it's very important.

Just briefly touching on this therapy related MDS and leukemia I mentioned. It's people who receive chemotherapy, radiation or both. It happens a lot in people who have lymphoma, Hodgkin's disease, breast cancer, ovarian and prostate cancer and it takes about five years or about 60 months to develop after the chemotherapy.

I have a couple really complicated slides right now, but these are the classification system. This is just to give you an idea of how complicated it is. This is an older classification system. You may have heard about the FAB. I always say it's the last time the French, American and the British agreed on anything and then in 2008 we had the WHO, the World Health Organization, MDS Classification. This was kind of like the really first robust classification we had since the FAB, but more recently we have a brand new MDS classification system and I think this is all going to be in your books that you got today. I didn't put this up with the intent that you can read this or I'm going to read this all to you, but just to give you an idea of how many things we have to look at and how many different subtypes of MDS you could be diagnosed with and to point out the fact that the classification depends on how much dysplasia you have, whether or not you have ring sideroblasts, whether or not you have increased blasts and then there's these other groups that we really can't classify because they just have low blood counts and may be sort of borderline dysplasia in the marrow. So, and that's something that you can go to your doctor to and ask or you can... and looking at these books that we give you that will help you to kind of figure out which group you're in.

And then there's other ways that we... there's other types of MDS that we see such as this therapy related I talked about. You can have myelofibrosis in your bone marrow. Does anybody know about that? Anybody have issue with that? Yeah. And then you can have... remember how I talked about how the marrow tends to be like really packed, but inefficient. There are some people with MDS that have hypocellular and it can look a lot like aplastic anemia which is another marrow failure disorder.

This is that IPSS I was talking about. (Attendee), I think you were asking me... or no, I'm sorry. Somebody... you were asking me about the prognostic scoring system. So, this is prognostic scoring system that I was talking about. It stands for International Prognostic Scoring System. The R means it's revised because this past year there was a new version of it came out. This just... what this prognostic scoring system does is it uses your cytogenetics, your bone marrow blast counts, your hemoglobin level, your platelets and your neutrophil count, absolute neutrophil count, to calculate a score and it will put you into one of five risk categories and, again, this will all be in your book and this is something that you may want to do when you go back and you look at your marrow at the time of diagnosis and kind of see where you fit in.

**Q17:** (inaudible 47:08 – 47:22)

**Virginia Klimek, MD:** Yeah, yeah, yeah. Good.



Remember I talked about how important genetics are? So, these are the genetics categories that we use in this prognostic scoring system and you can see how you could have very good genetics if you only had one chromosome abnormality or just one of these versus if you have multiple chromosome abnormalities and then you have these categories in between and your doctor or you can look at this and just sort of figure out what kind of cytogenetics you have and how that affects your overall prognostic score and, again, this should all be in your book as well and what we find is that when you use this score you can get an idea of without treatment, by the way, these scores are all based on will tell you what will happen if you don't have any treatment, how long your survival might be and your risk of developing leukemia.

Oaky. So, MDS is diagnosed. What's next? I'm going to go through quickly some general principles of treatment and then Amber is going to come up and talk a little bit more about the specific treatments and how they work.

So, whether or not you need treatment at diagnosis and what that treatment is is highly variable. You asked about what happens if you present with the MDS bordering on leukemia. We're going to want to treat that right away. We want to prevent it from developing into leukemia, but if somebody comes in with just anemia, I can monitor that patient, that person, for years without treatment just monitoring their counts. So, tempo of the disease is variable. You may not need treatment right away. We always have to monitor even if you're not receiving chemotherapy and it's really important to find out or to think about early on whether or not a stem cell transplant is an option. Anybody who's come to see me knows that I talk about it at the first visit because we know that transplant is the only treatment that we can give you that's curative. We'll talk about chemotherapy injections to treat anemia, but the only thing that we have in our (inaudible 49:41) to cure this disease is a stem cell transplant. So, we always want to know as soon as we can so we can make sure that we do that procedure if it's possible.

So, whenever we consider any treatment whether it's an anemia injection or a chemotherapy treatment or transplant just like if your cardiologist is picking a blood pressure medication for you, you have to consider the risks and benefits and you have to weigh both. Right? So, the risks... of course, the risks or side effects of the drug as well as travel and treatment time. Like who wants to go to the doctor seven days in a row and have your counts monitored every week and go into New York City. Whatever. You know what I mean? It's a big change in your quality of life to receive these treatments. So, you have to consider that as part of your... as you weigh your decision. On the other hand maybe if you're going to have a transplant you have a chance of being cured, some people say look, I want to give it a try. I just want to know that I gave it my best shot that I tried everything and, of course, everybody wants to feel better especially if you're anemic because when you're anemic you're dragging, you're fatigued. You can't do what you want to do and to get better disease control maybe as a bridge to transplant.

**Q18:** What is the age (inaudible 51:05 – 51:10)

**Virginia Klimek, MD:** So at Memorial Sloan Kettering we evaluate people up to the age of 75. We can't always transplant everybody that we evaluate, but we consider people up to the age of 75. One of the reasons we've been able to inch up the threshold is because we're developing newer techniques to do transplant that can be safer and also because we're able nowadays there are more ways to do a transplant. So, we can find donors from more people than we used to. Also and this is not an inconsiderable issue, but about six or seven years ago, Medicare decided that they would pay for it. So, if you look at tables of statistics showing how many people were transplanted you'll see an uptick around that time because before that Medicare wouldn't cover it and we had to go through appeal and appeal after appeal to try to get because we knew that this was something that would cure people, but if the Medicare wouldn't cover it and that was your insurance we couldn't do it. So, the last five to seven years has changed the number of people that we can transplant.

**Q19:** (inaudible 52:27 – 52:40)

**Virginia Klimek, MD:** Not direct. Not direct. Transplant is riskier as we get older. When we do transplants in people who are over roughly 65, we have to... the chemotherapy that we use has to be sort of chemo light. It can't be super intense. It can't be the same strength of chemotherapy that we would give to somebody when they're 40 years old. So, when you have to do those lighter transplants or you'll see them referred to as mini transplants or reduced intensity transplant. When we have to do a transplant with a reduced intensity regimen, it sometimes lessens the likelihood that the transplant will work because the chemotherapy is not strong enough, but we really don't have a choice because if we give therapy that's too strong then we cause more harm than good. So, it's...

So, the treatment options include something we call supportive care and Kelly's going to talk a lot about supportive care and symptom management. Growth factors which are injections that stimulate the bone marrow to work harder to make normal cells, Amber is going to help me talk about that a little bit more, too. There's a class of drug called hypomethylating agents. I think there's a couple of people in the room had questions about Vidaza or 5-Azacitidine and its cousin drug Decitabine. Lenalidomide. Have people heard about Lenalidomide or Revlimid? Revlimid is the other name for that. That's primarily a drug for anemia. There are drugs that we can use that are called immunosuppressive drugs. They suppress your natural immune systems and that can sometimes help people with MDS. Many people don't hear about this and many people are not treated with these drugs nowadays. It seems like since Decitabine and Vidaza became available about 10 years ago the use of these drugs have sort of dropped off not because they don't work, but frankly a lot of people can't tolerate these drugs. There's a lot of side effects and they don't seem to work any better than like 5-azacitidine or Decitabine. We always consider clinical trials even for the first treatment that you receive and as you were talking about with the leukemia if you have the MDS that's with the high blast count that's verging on AML range, it's not unreasonable to use just leukemia therapy at that point and then, of course, allogeneic stem cell transplant.

Amber, are you going to...? I don't know how much you're going to talk about...

**Amber King:** (inaudible 55:40)

**Virginia Klimek, MD:** You're going to start with growth factors?

So, supportive care, I think, and Kelly and Amber will elaborate on these, too. It's really what I call the cornerstone of treatment whether you're just diagnosed and you're just being monitored or you're on a clinical trial or you're receiving AML chemotherapy, supportive care is an essential part of your management. That includes monitoring, transfusions, antibiotics to prevent or treat infections and possibly iron chelation depending on how high your ferritin levels are. I'm going to let Amber talk a little bit more about this because she has some really great pictures and I don't have pictures.

I wanted to touch a little bit on chelation because a lot of people have questions about iron chelation. If you're needing a lot of red blood cell transfusions or in some cases your ferritin level can be elevated at diagnosis particularly in... we see it commonly in people who have the ring sideroblast subtype you can have an elevated ferritin at diagnosis. There are trials that have been done and are ongoing to see if iron chelation, removing that excess iron from your blood that you accumulate as a result of the transfusions, if that affects your bone marrow function, if it affects your survival and although there's data suggesting that iron chelation improves survival and improves blood counts the jury is still a little bit out because those studies that were done were kind of looking back in time. They're called retrospective studies and there's a lot of bias in those studies and so what we really need is these prospective studies that are ongoing to get the answer to that question about how important iron chelation is for a given person and this is an example of a prospective clinical study that's been going on for years. It's not open anymore. I think it's closed and they're not putting patients on it, but they were trying to compare this oral chelating agent to placebo to see if it prolongs their survival.

Amber, you're going to talk about... Again, I think she's got better pictures.

The one thing I'll point out here is that Revlimid was FDA approved for people with this deletion 5Q that chromosome abnormality that you were talking about because it made people transfusion independent to the tune of about 70 or 80 percent of the time. So, it's a fantastic drug for people who have... especially just isolated deletion 5Q and they have anemia. It really helps the anemia and this is just the schematic showing the trial. We actually looked at this drug, Revlimid, in people who had in addition to 5Q who didn't have 5Q. The response rate is there, but it's lower, about a quarter to a third of patients will have an improvement in their red blood cell counts for their anemia.

This is immunosuppressive therapy. The point I wanted to make about this immunosuppressive therapy is that it tends to work... this is the response rate over here and this is your age. You can see as you get over the age of 60 the response rates are not as good. If we use them we tend to use them in younger people and this is just a summary slide showing how 5-Azacitidine or Vidaza and Decitabine. This is multiple trials that were done and it shows that the response rates are somewhere around 50 percent. Amber's going to talk a little bit more about the way these drugs work.

I'm just going to close with a few sort of general slides, slides just kind of talking about some general principles and challenges with MDS therapy. One of the things we struggle with and which I try to explain to my patients is that you have to go through like with for Vidaza. You have to go through like four to six cycles to give it a chance to work. There's really no way to know a priori, before you start treatment. There's no way that I can say okay, you're going to be the one that's going to respond and you're going to be the one that's not going to respond. We can't say that until we actually give the drugs and try it. It's possible that if you have increased blasts and you have low blood counts that the counts will go up and the blasts will go down or just maybe the blasts will go down and the counts will stay low. So, the responses are variable and we still don't have a good way to predict who will respond. So, you just sort of get through for in the case of Decitabine, four months of treatment or with Vidaza four to six months of treatment and see if it works. Then once the drug works we just continue the treatment as maintenance therapy. Is there anybody in the room familiar with what I mean by maintenance therapy? I know you are. But the way to maintain the response is just to continue the drug indefinitely until you lose the response, but we... for a given person we don't know how long that response will last and then the big problem is that ultimately everybody will progress on MDS therapy if they don't have a stem cell transplant. So, even if the Revlimid is working or even if the Vidaza or the Decitabine is working, eventually it will stop working and that's just a terrible deficit that we're working hard to understand and fix, but we're not there yet.

This is just a summary slide showing that there's a variety of treatments that we can use for low neutrophil counts, for anemia, for low platelet count and that stem cell transplant can be considered for any one of these problems as long as the disease is advanced enough to justify the risk of the transplant.

I then just wanted to highlight how we choose the treatment. Right? So, I've talked about a lot of different treatments. I've told you about how variable the disease is from one person to another and this is just to sort of highlight how if you do have a deletion 5Q abnormality you may be more likely to respond to Revlimid and that it tends to be a good prognosis disease. If you have the RARS subtype you may be more likely to respond to a combination of growth factors rather than just like Procrit or Darbepoetin alone and that if you have multiple chromosome abnormalities you need to be watched more closely or you might have to jump into treatment right away.

**Q20:** (inaudible 1:02:34)

**Virginia Klimek, MD:** Yes, but right now the way... whenever we... oh, actually there is one instance where we combine that's FDA approved and it's been proven to work, but generally combinations are best done in a clinical trial because we don't know if they work and we know that there's probably added toxicity with the combination. So, we try to be careful about that and we study it in a clinical trial.

Remember I told you that we have to think about transplant early? So, when we think about transplant early, we have to say okay, yes, is transplant an option or no and if it is we do things called HLA typing. We refer the person to a transplant physician. We may be using chemotherapy like Vidaza or Decitabine to control the disease while we're looking for a donor or if you're lower risk, if your IPSS score shows that you're low or intermediate 1 risk we just may watch you and not do transplant until later time. If somebody's not a transplant candidate because of medical issues or they don't have a donor then we don't have it... because we don't have a curative option, but there are treatments that we can use to prolong your survival like supportive care, these anemia injections I referred to before, Vidaza or Decitabine, these hypomethylating agents and especially when somebody's not going to transplant we really need to make sure we encourage the use of maintenance therapy continuing these drugs to get the most... the longest response that we can from them.

And I think... Yes, I think this is my last study. So, one size does not fit all depending on whether or not you come walk in to your doctor's office with lower risk disease or higher risk disease, high blasts, low blasts, anemia, low platelets or all of the above, your treatment options are going to be different and the way that the doctor is going to sequence those treatments is going to be different and we should always be looking at clinical trials because we want to do better with the treatments that we have. We want to improve the response rates of the drugs we already have and find new drugs to treat this disease.

I'm going to skip over this because I already talked about this transplant. No standard treatment algorithms and then I think I'm going to pass it over to Amber, but I think we have time for some questions.

**Q21:** (inaudible 1:05:02 – 1:05:32))

**Virginia Klimek, MD:** Possibly. So, the pattern... So, I'm glad to hear that it's working and what...

**Q21:** (inaudible 1:05:41) bone marrow since they started. (inaudible)

**Virginia Klimek, MD:** So, when people have a response to the chemotherapy either their blood counts are improved and/or the blasts go down if the blasts were a problem to begin with and the



disease progresses while you're on it, the Decitabine. Two things can happen. Your disease could go back to looking the way it was when you started the Decitabine. So, let's just say if you have high blasts to start with and the Decitabine brought the blasts down when the Decitabine stops working you may see the blast counts go back up like they were before or the blasts could stay low, but the blood counts will go lower. You know what I'm saying? So, there's different patterns of progression when you're on these drugs. So, just to say it again the disease could go back to looking exactly the way it was when you first started the chemotherapy or it could kind of morph into something different. Like I said the blasts could stay low, but all of a sudden now your platelets are super low and you didn't have that problem before.

Yes?

**Q22:** We're in a watch and wait mode. What can be done (inaudible 1:07:00) in an attempt to fight off the disease (inaudible)?

**Virginia Klimek, MD:** So, what I would say is that if you're in a watch and wait phase it generally means that... what that means is that you don't need treatment. So, I'm going to kind of give a little bit of an explanation for why you don't... what sort of the triggers are for treatment and then I'll answer your question. So, when people... does everybody remember what a neutrophil count is? Neutrophils are your infection fighting cells. When we talk about something called an absolute neutrophil count or it's abbreviated ANC. When the absolute neutrophil count is less than .5 or 500, that's when people tend to be more at higher risk for infection. If your neutrophil count is .5 or lower and you're starting to get into trouble with infections that's a trigger for starting chemotherapy because we know that your immune system is weak and if we don't treat you and try to improve that blood count that you're just going to start having more trouble with infection, but if your neutrophil count is .5 or higher or even if it's .4 and you're not having infections what does that... that tells us that your immune system is doing an okay job. You're able to avoid getting excessive infections and that your immune system cells are working. So, we don't routinely give medicines to boost your immune system when the immune system seems to be working fine. That's one thing, but the other thing I will say is that there is really no good proven medicine that has been shown to boost the immune system that's available to treat MDS. Now, there are things... and actually Amber is going to talk a little bit about that because I think people are always looking for something like this, but unfortunately we don't really have a good drug to boost the immune system in a way that changes the actual bone marrow function. There are injections and, again, I mentioned as part of the supportive care there are growth factors that you can receive called Neulasta or Neupogen. These are the commercial names for them. When we give those shots it boosts the neutrophil count or neutrophil count production in many... not all, but many patients with MDS. We don't routinely use those injections because when we studied this many years ago and we gave those injections to people even if it boosted the neutrophil count it did not reduce the risk of serious infections and it didn't change the survival. So, we don't use those routinely, but if let's say if anybody... I don't know if anybody here has experience with this, but let's say if you got



admitted to the hospital with pneumonia whether you were on chemotherapy or not and if your neutrophil count was low we might give that to you for a short period of time to kind of boost your immune system just in case it helps. We don't know that it helps, but we use it in those sort of emergency situations just on the chance that it will help your immune system to fight off whatever infection you have, but we don't use it prophylactically to prevent infection.

There's somebody in the back (inaudible 1:10:25). I'm sorry. Yeah?

**Q23:** Could you go back to the slide just to clarify something with the genetic abnormality?

**Virginia Klimek, MD:** How far back do you think it was?

**Q23:** It was probably towards the middle of your talk. It's the IPSS score.

**Virginia Klimek, MD:** Oh, the one with all the different colors?

**Q23:** Yeah.

**Virginia Klimek, MD:** Yeah, yeah, yeah. Let me see if I can find it fast for you.

**Q23:** That one. So, under the single, double and complex... on the yellow before. That includes where you put single it says deletion like 3Q examples including... so, any two chromosomal or any three?

**Virginia Klimek, MD:** So, any three...

**Q23:** Not specific.

**Virginia Klimek, MD:** Any three. A double if it includes either a Monosomy-7 or deletion 7Q or any single such as this derivative 3Q.

**Q23:** Oh, so that's the specific. So, the single would be the three, the double would be seven plus something else and okay. Alright. Got it.

**Q24:** (inaudible 1:11:47 – 1:11:54)

**Virginia Klimek, MD:** So, what (Attendee) is asking if gene mutations are factored into this? So, not yet. Not yet. There is a multi-center international effort going on now and it's actually being led by Dr. Elli Papaemmanuil at Memorial Sloan Kettering. She is sequencing bone marrow samples from patients all over the world looking at about 200 genes and what she's going to do is take those genetic mutations and match them up with the chromosome abnormalities that those individuals have and then plug them into a big statistical model to see if

having any one or more of those mutations adds to this in terms of the prognostic score. So, that's underway and it's a tremendous effort and it's going to be important. It's going to be a very important way for us to use this mutation information that we're seeing now.

**Q25:** (inaudible 1:12:57 – 1:13:13)

**Virginia Klimek, MD:** That's a really common question because we're talking about blood and bone marrow. Right? So, but actually the blood type matching isn't important. It's something called HLA typing and it's based on your white cells actually. So, if it's the same blood type... so it doesn't have to be the same blood type.

**Q25:** (inaudible 1:13:32 – 1:13:36)

**Virginia Klimek, MD:** Potentially. So, a transplant can explain to you what his best... what your best stem cell source might be whether it's a brother or a sister or some unrelated matched volunteer in the donor registries or cord blood. We were talking a little bit earlier about how transplant has changed in the last five to 10 years and one of the reasons that it's changed and we're able to do so many more transplants is because we have more sources for stem cells. Cord blood is becoming a very important alternative to having let's say, a living healthy brother or sister. So, yes, it's possible that you could have a cord blood transplant, but they may prioritize a sibling or a better matched unrelated donor over the cord. So, it depends on... a transplant team will look at all of your transplant options, all of your stem cell source options.

Yes?

**Q26:** (inaudible 1:14:42)

**Virginia Klimek, MD:** I am. I'm going to talk about that at the end. I know. That's one to watch. That's definitely one to watch. Yeah. Yeah.

**Q26:** (inaudible 1:14:55 – 1:15:03)

**Virginia Klimek, MD:** I can talk to Lea. I know this is being taped, but I'm not sure about the... I don't think they're capturing the video on this.

**Q26:** (inaudible 1:15:18 – 1:15:25)

**Virginia Klimek, MD:** Okay. Yes?

**Q27:** (inaudible 1:15:28) recommend that (inaudible)

**Virginia Klimek, MD:** So, does maitake sound familiar?

**Q27:** Yes.

**Virginia Klimek, MD:** Okay. Maitake. So, there is a maitake... it's a specific extract from maitake mushrooms. There was huge... Did you ever see them? Have you ever seen one? They're ugly, but they're like... do you have a picture on your slide? No. She's got really good pictures. So, yes, and you've probably seen... if you've looked for it you can find it in a natural food stores and something like that.

**Q27:** (inaudible 1:16:06 – 1:16:14)

**Virginia Klimek, MD:** So, and this is actually to get to your question, too, about things that can improve... oh, okay. Okay. So, yeah. There have been studies done that suggested that there was a specific extract of maitake mushroom that worked a little bit like Neupogen, this injection I was talking about, the one that can boost neutrophils and actually... we actually published a paper... it's a couple years ago now I collaborated with the Integrative Medicine Service at Sloan Kettering and we have a company in Japan make this like pharmaceutical grade extract for us to study this and so we gave it to people who had MDS and we did a lot of laboratory studies along with it and it didn't increase the number of the neutrophils but based on the studies that we did in the laboratory it seemed to maybe enhance the function of some of the immune system cells. A follow up study hasn't been done because that company just didn't want to or have the finances to do it. So, what we need to do is actually do a larger study and follow people for a longer period of time and I will say that when we did that study we didn't know if it was going to help people. So, we gave it to people who weren't having infections because we didn't want to... if somebody was having infections remember I told you that's when you would start treatment. So, we don't want to... if somebody's already having infections and complications from their low counts we don't want to put them on a treatment that we don't... where we don't know... where we don't know if it works. So, the initial study was in people who have low neutrophil counts, but they were well. They weren't having any problems just to sort of show that it was safe and to see if we could pick up any activity in the laboratory. The next study to do, the important study to do would be to say okay, we have people with a low neutrophil counts and they really... they don't want or they're not a candidate for regular chemotherapy, but we can try this mushroom extract instead and see if over time the frequency of infections is lower than people who don't take it. That's the study that would have to be done. It does cause some GI problems, stomach problems.

**Q28:** (inaudible 1:18:35)

**Virginia Klimek, MD:** Yeah. It's not the easiest thing to take.

Yes?

**Q29:** (inaudible 1:18:45) and what we do was try to (inaudible) exercise (inaudible) it's unbelievable so I can say that's the (inaudible) really take care of yourself and he's been doing great. He does have a lot of (inaudible), but we just deal with that and in the meantime we just live our life and do what we can do and it's so far so good.

**Virginia Klimek, MD:** Now and what you'll see is there's a lot of variability. Some people will tolerate a hemoglobin of 6 – 6 ½, but some people will start feeling short of breath when it's 9 ½. So, everybody's a little different and what we try to do is we try to tailor our transfusion approach to the individual because we don't want to give... look, transfusions have complications. So, every medicine including... and transfusions have side effects. So, we don't want to give it if you don't need it.

**Q30:** (inaudible 1:20:05) concerns of (inaudible) levels. The doctors (inaudible) but does it really have any effect? (Inaudible) or does it matter?

**Virginia Klimek, MD:** So, it's a... we debate that because it's been hard to do with study and you have to... if somebody is needing transfusions over a long period of time in order to do a study to see if it makes a difference in somebody's survival or their blood count production over time you have to do a study that randomizes one group to receive a chelating agent and another group is not getting anything. I did point out one study that was trying to do that. Frankly, they had a hard time getting people onto that study because people don't want to be on a placebo and many doctors feel uncomfortable about it, too. So, it's been hard to prove it definitively, but some of the retrospective data suggests that the chelating agents will help with prolonging survival, but it just may be that the people who need... people who have high ferritin levels who need a lot of transfusions their disease just may be different than somebody who doesn't get on it... who's not on it. So, it's hard to prove it unless you do this prospective study. The NCCN guidelines, the guidelines that are generated in the United States for MDS they've recommend considering chelation therapy when the ferritin level is around 2,500 or higher and that's based on (inaudible 1:21:43) data where the data is much better. You'll see other guidelines where they suggest that you start the chelation therapy over 1,000, but what that should tell you is that there's uncertainty even among the experts. That's what that should tell you. You're welcome.

**Q31:** (inaudible 1:22:00). Any comment upon whether the blood (inaudible)

**Virginia Klimek, MD:** So, red blood cells live on average about 21 days, 21 days. So, they live about three weeks once they're produced. So, that's why there's a shelf life. They can't... because if you store them for too long the cells will naturally die. So, I think what you're getting at is and I've been asked this before is if you get a unit of blood from somebody that was donated two days before, I think... Yeah. I think it's going to boost your hemoglobin more than if it's 21 days old. Is that what you're wondering like...?

**Q31:** It sounds like (inaudible 1:24:04)

**Virginia Klimek, MD:** It's possible.

**Q31:** it's not going to do anything.

**Virginia Klimek, MD:** No, it will. It will. Yeah. But just so you know they store it... they don't store it... it's not like out in the open. It's stored in a way that preserves them, but I'm just trying to give you an idea these are cells that are not... it's not like in stasis. They will die off and inside the body the average life is 21 days, but the longer... the closer they get to their expiration date the fewer effective living cells you get and I... people have asked me this. Well, can't I just go by the blood bank director and say I just want... give me only the freshest components that's... yeah. I think they try to... So, we have a blood supply problem in this country. So, what I would say is that they have to maximize the use of this precious resource. So, if they gave... So, they have to use the blood that's approaching the end of its shelf life. They have to and I have not been able... I don't know of any policy or and maybe it's a study that just hasn't been done that for MDS patients it works better to consistently get fresher, but it's... unfortunately it's probably out of your doctor's control what unit you get because they have to use whatever's on hand and remember they have to match the blood for your type. So, if they have a unit that was collected three days ago, but the only unit they have in stock that matches your blood is 21 days old you're going to get that one because we can't give you the other one. So, it's probably a combination of factors.

**Q32:** (inaudible 1:25:51)

**Virginia Klimek, MD:** No, shorter. Shorter.

Platelets, the platelets are a little bit of a different thing. They're developing additive solutions that can be mixed in with the platelets to make them last longer and to also reduce the chances of platelet reactions. If anybody here knows you can have transfusion reactions to blood or platelets. So, stay tuned, but in the years to come you're going to start hearing more about these platelets with additive solutions that reduce the risk of transfusion reactions but also prolong the shelf life and make them more stable.

**Q33:** (inaudible 1:26:34 – 1:26:45)

**Virginia Klimek, MD:** Well, it's the American Red Cross. Your local blood center.

**Q33:** (inaudible 1:26:54)

**Virginia Klimek, MD:** Yeah. Yeah. Yeah.

**Q33:** (inaudible 1:27:01 – 1:27:05)

**Virginia Klimek, MD:** Yeah, but especially in the summer months. People are on vacation, they're out doing what they do and it's typically in the summer months where the supply dips. We're really fortunate at Sloan Kettering where last I heard about three-quarters of our supply is provided by our employees and also the families of our patients. They come in and they donate. It's just amazing. It just gives me goosebumps to think about it because it's just... I mean, we have access to the American Red Cross in our local chapter, but we're really fortunate to have a really deep inventory because of that, but it's amazing. Our patients' families, I mean, I... we had a fireman come in the other day and the whole fire house came and they donated. It's just amazing. So, yeah. That's... I agree with you. I think more advocacy or more visible advocacy is important for that.

Yeah?

**Q34:** (inaudible 1:28:00 – 1:28:08)

**Virginia Klimek, MD:** It may depend on what type, but if you call the blood... the donor center and you can ask. You can ask. There are a lot of restrictions for donating blood because they want the supply to be safe. There's age restrictions. There's a lot.

**Q34:** (inaudible 1:28:22 – 1:28:50)

**Virginia Klimek, MD:** I'm sorry. I didn't hear the first part of the question.

**Q34:** (inaudible 1:28:53 – 1:29:14)

**Virginia Klimek, MD:** To let the doctor know what the...

**Q34:** (inaudible 1:29:17 – 1:29:22)

**Virginia Klimek, MD:** Oh, I see... No, I see, but... I'm sorry. Now, I understand. It's very rare that something is inherited that you can pass onto your children. I think the things that would tip a doctor off and maybe... where the doctor might recommend genetic counseling is if there tends to be a lot of cancers clustering in their family in addition to MDS. It might signal that there's an issue there if there's multiple cancers, but generally just MDS by itself... although there are people who are interested in studying families where maybe there's not multiple cancers, but let's just say two brothers have MDS or a father and a son have MDS. There are research groups throughout the country that would be interested in having blood or skin samples to test... to see if they can identify some predisposition gene. You know what I'm saying? So, it's a very much still a research question, but if there... if MDS tends to cluster in a family there are definitely groups and I can get information to you that are interested in getting samples so that maybe even



if we can't give you the answer then you can be part of the... you can be part of the answer. Do you know what I'm saying but the other research? Okay.

Maybe we should move on to Amber.

This is Amber King. She's our Pharm.D. She works with me at Memorial Sloan Kettering at our Manhattan campus and she's joining us today. She came all the way out from New York City to join.

**Amber King:** Thank you for having me.

So, I want to go over briefly, Dr. Klimek did such a great job to talking about what treatments do you use and kind of my job at main campus and all of the pharmacists available talk to patients when they started about some of the side effects, how it's given and kind of what to expect. So, these are slides are kind of a brief overview of those treatments and at the end I have a slide briefly talking about herbals and supplements that we get commonly asked about and I'll open the floor for questions afterwards.

So, first I'll start with GCSF, or granulocyte colony stimulating factors. So, this is just a fancy term for drugs that stimulate neutrophils or the infection fighting portion of the white blood cells. That two that we use most commonly are called Filgrastim or Neupogen and then Pegfilgrastim or Neulasta and you'll see how the end of the name because the Filgrastim is one that we give frequently because it lasts a short period of time and Neulasta lasts a long time. So, we give the injection every two weeks.

So I kind of have broken down the slide. To the left you'll see the Filgrastim. They're both injections. The Filgrastim can be given subcutaneously or just under the skin in the abdominal or stomach tissue or sometime it's the legs. It can be given by the nurse or sometimes we send patients home with prescriptions so they can inject themselves. The dose is based on your weight and so everybody's dose will be a little bit different, but they kind of come in standard sizes. So, you'll kind of see either 300 micrograms or 480 micrograms if you're a tall or a larger person. Like I mentioned before, it's given frequently because the drug doesn't last long and it can be given once a day or sometimes up to twice a day depending on your blood counts and the clinical team's decision based on your numbers. On the right hand side I mentioned the Pegfilgrastim. So, there's a special feature of the Filgrastim that we've attached to the drug that makes it last a really long time. So, you don't have to come in frequently and often. So, if deemed clinically appropriate this one's given under the skin or subcutaneously and, again, it can be given by the nurse or you can get sent home with a prescription to give it to yourself at home. This one is always dosed flat. So, it's either going to be a six milligram dose or sometimes a three milligram dose. So, the doses kind of don't vary as much as the Filgrastim does and like I mentioned before it lasts long in the body. So, we average give it every two weeks, but there's sometimes we can give it a little bit earlier, every 10 days. So, you can see in certain scenarios if you're on

chemotherapy we can't use Neulasta on everybody, so sometimes we have to use Filgrastim if we're just seeing a little small boost for a short period of time.

I've shown some pictures here as Dr. Klimek kind of noted before. These are the injectors and how they come. So, you see on the bottom of the screen that's the IV Neupogen. Usually, people that are in a hospital we can give it IV because the nurse can draw it up. If it's something that we give in the clinic it's often the auto injectors, ones on the top, and you can see the two different strengths that it comes in based on the dose we calculate based on your weight and on the right you can see the Pegfilgrastim or Neulasta and that's a longer acting injection.

Some of the side effects that kind of we counsel patients on are bone pain. So, as Dr. Klimek mentioned before these kind of stimulate the bone marrow to produce cells and the pain tends to happen in the biggest bones because that's where the most marrow is. Sometimes people kind of feel kind of aches and pains and they can kind of happen in the biggest bones, the ones in your arms, the ones in your legs and sometimes the big bone in your chest, the sternum. So, interestingly what we use for bone pain can be an allergy medication. So, when the immune system is revved up and assimilated it actually releases histamine. So, if you think you use an antihistamine this can definitely offer some pain relief and there's virtually really no side effects. So, things like Claritin or Zyrtec. So, we often recommend this to these patients up front or if they tend to have issues with the medication we kind of can have them take it after the injection. Usually, if people even get the bone pain it kind of goes away a day or two after the injection. That being said there's a very few select group of patients that may have a more severe bone pain and sometimes we can use more powerful pain medications after discussion with the team such as oxycodone. Again, it is an infection but it's under the skin usually. So, it's kind of a tiny pinch and typically can kind of feel some irritation a little bit after the injection, but some cooling packs help it go away within a few minutes and then finally if we send patients home with a prescription there tends to be insurance issues sometimes. So, we end up giving it to people in clinic, but that being said if it's a prescription that's sent home we might ask for an authorization and copay issues. So, that's kind of barriers why everyone doesn't get this at home there's sometimes the insurance won't cover it. Any questions about the GCSF so far?

**Q35:** (inaudible 1:35:54 – 1:35:57)

**Amber King:** You can use Benadryl which is Benadryl tends to make people more sleepier and it's a (inaudible 1:36:02) called anticholinergic. So, it can make people dizzy and dry out the mouth. So, we kind of tend to use the newer generations like Claritin and Zyrtec because they'll make people sleepy and the side effect profile is less, but in theory if you take Benadryl for other reasons and you're fine that can be an agent that can work just as well.

**Q36:** Is there any limit of much of this you can have? I know that (inaudible 1:36:27) sporadically because there's a concern that (inaudible).

**Amber King:** So, that's an excellent point. So, there's a fine balance. So, there are certain stages and certain type of MDS in which this is used in combination with other growth factors and there are certain points in which depending on how much of the blast percentage of disease that we have to balance and revving the immune system up too much and kind of protecting you from infection. So, the short answer is yes and it depends on where you are and what type of subset of MDS. So, it's used to also stimulate the neutrophil count either in response to chemotherapy, which I'll get to later or sometimes just that the neutrophil count is low just a temporary boost. Okay?

Next, I'll go to the hypomethylating agents are also known as our low intensity chemotherapies. So, the two that we use in MDS are called Azacitidine and the brand name is Vidaza and the next one is Decitabine also known as Dacogen and so the mechanism of action is very complicated, but to summarize it up these kind of block the essential stuff in DNA that helps the rapidly dividing cancer cells for really quickly and so it hypomethylates or takes one of the building blocks of DNA replication to slow the growth of the cancer cells down and so you see on the left and the right I've defined Azacitidine and Decitabine respectively. So, on the left we have Azacitidine or Vidaza. This one can be given either intravenously or subcutaneously under the skin. If you get an IV infusion it's relatively quick compared to other chemotherapies usually infused over 10 minutes or up to over 40 minutes depending on what institution you're being given the drug at and the subcu injection is pretty quick. It can be given in the thigh, the stomach or the upper arm depending on where the nurse or you would like the drug injected. So, Azacitidine is distinctly different than Decitabine in a few ways but most notably how often to give the drug. So, in the chemotherapy cycle the first seven days if you're getting Azacitidine involves you actually getting the drug infused. So, in days one through seven you'll get the Azacitidine. There's some other places and institutions which instead of giving seven days in a row they'll give you five days, Monday through Friday, give you the weekend off so they'll finish off the next two days in the week if that works better in your schedule, but essentially want to get a total of seven days of active chemotherapy for you in your overall 28 day cycle and this drug was convenient. It could be given either outside of the hospital or inside of the hospital depending on your and your medical team decide. On the right we talk about Decitabine or Dacogen. This one's only given intravenously and the infusion is a little bit longer. It's over one hour and it's different than Azacitidine in how it's given. This one is only five days of active drug per cycle. So, days one, two, three, four and five you'll get the IV infusion and you'll let your counts kind of go through the cycle of 28 days and, again, this can be either given inside the hospital or outside of the hospital.

Saw you had another question.

**Q37:** Yes. I take (inaudible 1:39:37) but I take in pill form five days. Is that because (inaudible)

**Amber King:** Clinical trial?

**Q37:** (inaudible)

**Amber King:** Exactly. So, the only available, commercially available versions for right now are either IV or if you're taking Vidaza. It's either intravenous or under the skin, but exactly. There are these agents that are coming in pill form which would be even better for our patients and more convenient, but right now available we just have the injectable versions.

**Q38:** (inaudible 1:40:06)

**Amber King:** Well, actually I have a brief slide on the next few slides about overall what to expect and what the goal is. So, I'll kind of go over that.

**Q38:** (inaudible 1:40:20)

**Amber King:** Sure. No problem.

Before I get into that I'm going to go over some notable side effects. So, for one thing it's a low intensity chemotherapy. So, the question I always get asked the first is... Oh, (Attendee). Hi, (Attendee).

**Q39:** (inaudible 1:40:37) the first two cycles was like a (inaudible) Towards July 4<sup>th</sup> they're doing four days.

**Amber King:** Total?

**Q39:** Yeah. I mean, should I mention to the doctor that...

**Amber King:** You're skipping a day kind of?

**Q39:** Yeah.

**Amber King:** So, I'm assuming where you're treated they don't open on the holiday?

**Q39:** They don't open on the holidays or weekends.

**Amber King:** Okay. So, overall on average we try to stick to the cycle period, but such is life is that sometimes we have to make up the doses or cut off the doses. So, I'm hoping in the discussion just mention that you have a concern where you're getting four of the five days, but overall like Dr. Klimek mentioned briefly this is kind of a long game. You want four, five and six cycles to get the overall benefit. So, in the long scheme of things it's hard to determine if missing that one day of Decitabine will kind of have some sort of adverse effect, but you're right. Correct. Usually, it's five days total drug. Now, if that's five days on time versus five days

at some point it's kind of the convenience package because you want you to be able to kind of have flexibility and freedom of being able to kind of do your activities without being interrupted for the chemotherapy kind of thing, but it does happen often where sometimes we have to finagle the schedules to work with your vacatoin and other events that happen in life.

**Q39:** I take like Vidaza. (Inaudible 1:42:07)

**Amber King:** Just five days?

**Q39:** (inaudible)

**Amber King:** So, and is that the five days that's what you and your doctor decided from the beginning or did you have seven and kind of...?

**Q39:** (inaudible 1:42:19)

**Amber King:** Five. So, the FDA approved way and the most common way to give it is over seven days and there's some distant regimens where the doctor can play with the dose and give a larger dose over a shorter period of time and sometimes people who have a couple of cycles and have issues tolerating it, infections, nausea, other side effects, we sometimes can play with the dose in the discretion with the patient, but the best way to give it and the most documented way to give it is seven days of Azacitidine and five days of Decitabine. That being said between your numbers, your bone marrow and other effects that are just based on you there could be ways to be flexible, but overall and conventionally Azacitidine is usually seven days and Decitabine's usually five.

**Q40:** (inaudible 1:43:08)

**Amber King:** Yeah. Sure.

**Q40:** (inaudible 1:43:10) because the reality is (inaudible) and we'll also say that sometimes we still keep it on a holiday because every day it's enough (inaudible)

**Q41:** (inaudible 1:44:40)

**Amber King:** Okay.

**Q42:** One more question.

**Amber King:** Sure.

**Q42:** What is considered a high dosage of the (inaudible 144:49) high dosage?

**Amber King:** A high dosage?

**Q42:** I'm just curious, the size of the needle, milligrams.

**Amber King:** Oh. So, what the usual dose we use is for Vidaza is 75 milligrams and it's something meter squared or a calculation based on your body surface area. That's the conventional dose. Now, depending on...

**Q42:** I'm getting (inaudible 1:45:10)

**Amber King:** Total. Right?

**Q42:** Yeah. The needle.

**Amber King:** So, that's kind of based on what your calculation of your body size is because everyone's dose is the same weight base and it's just if you're largest the drug distributes differently. So, we have to take a standard number and multiply it by your number. So, you may get 174. I may get 150. Someone else might get... so, it's kind of the actual dose you get is different, but the way it's calculated is the same. So, proportionately everyone's getting the same amount of exposure.

Okay? Any other questions before I move onto the side effects?

**Q43:** Are you going to (inaudible 1:45:48) low blood counts.

**Amber King:** I am. Yes. Excellent.

So, briefly I touched upon because I think the most common question people ask me when they start this medication is nausea, but there's kind of stigma about chemotherapy what we see on TV or sitcoms or read about or even patient experiences with our family and friends and this is overall considered the low intensity regimen. So, nausea's extremely uncommon. Roughly about 10 to 20 percent of patients actually report nausea with these both Azacitidine and Decitabine and so that being said if patients do experience nausea there's a myriad of different medications that we can try both after the fact or in the cycles or even before we get to chemotherapy to prevent nausea from happening. So, I just put one popular medication on this slide, but there's probably 10 or 20 different (inaudible 1:46:36) of how to give this and it's called Zofran or Ondansetron and it's usually given up to every... to three times a day if you need it and sometimes people could even get therapy before they start the chemo cycle if they found they had a lot of nausea with the first one, but like I said overall very well tolerated regimen. People kind of get the infusion and then go do their work or daily activities afterwards.



So, I guess the question on everybody's mind is the low blood counts. There's some people ask is I already have low blood counts kind of why are we making this worse and so the overall intent of this therapy is like I mentioned it's kind of modifying the DNA and destroying how the MDS cells are proliferating. So, the long goal is kind of destroy these to overall help the new fresh bone marrow kind of grow and ultimately lead to normal counts. That being said in the process these agents do mostly affect rapidly and kind of deranged MDS cells, but the good cells do get hit as collateral damage especially in the beginning and so what the side effects are is that it causes kind of myelosuppression which is a fancy word for is it suppresses the bone marrow for a temporary period of time and this affects only the white blood cells, but the red blood cells and the platelets and so when I think therapy cycle it's the time it takes for you to get the drug infusion, for your counts to fall and the lowest point with these therapies are that your counts are likely going to go is 10 or 14 days after the start of therapy also known as your nadir. Now, during this time your white blood cells, red blood cells and platelets will be low. So, your doctor might prescribe you a red blood cell transfusion, platelet transfusion and to help the white blood cells out we might give antibiotics, things to protect you and do the job of your infection fighting cells until they recover. So, the time it takes for the drug... for the bone marrow to recover after the therapy is usually it starts inclining around the 21<sup>st</sup> day of the cycle or 21 days from your first day of drug and on average we expect the bone marrow to go down and come back up on the 28<sup>th</sup> day. That being said a lot of people can take longer to recover because it depends on what sort of grade of MDS you had, how low your counts were in the beginning and if you already had therapy for a prior cancer and your bone marrows are even exposed the same. So, don't be surprised if you don't get chemotherapy every 28<sup>th</sup> day on the dot because sometimes it takes a little bit longer to recover. The ultimate goal is that these chemotherapies are going to destroy all the bad MDS cells and make way for the good bone marrow to grow and that usually takes about four to six cycles and so overall that's kind of the goal of these agents is to clean out the bone marrow to make room for the good cells to grow back and so we kind of... we always expect your counts to go low because the chemotherapy is going to sort of get rid of all of the cells, but then the good cells are not as sensitive to this drug effect because they have normal DNA replication and so they will... we expect them to go back down the 21<sup>st</sup> to 28<sup>th</sup> day if that makes sense.

**Q44:** And you go back and start all over again.

**Amber King:** Exactly.

**Q44:** So, if you're on a four week cycle, you get to the 21<sup>st</sup> day and then you got a week then you start again then it goes (inaudible 1:49:49)

**Amber King:** On average. Exactly.

**Q44:** I've been living with this for a while now and I keep debating it in my head. It's almost like you're on a merry-go-round. You take, the Vidaza, to (inaudible 1:50:04) take the Vidaza to

reduce my transfusion dependency and as counts go down... and my counts really drop. I'll give you an example. I had a transfusion this past week. On Monday the day one that I was having my first Vidaza treatment, my count was 8.4. Now, for some people that's very low. I can get down to a seven before I need a transfusion. Two days later I went to have that follow up CBC. It was down six (inaudible 1:50:33). In two days mine dropped down to where I had to get a transfusion and this is kind of the cycle that I go through and that's why I think (inaudible) if both of my doctors I kind of asked them to extend at least five weeks so it didn't (inaudible) the 21<sup>st</sup> day, seven days later I was starting all over again with the transfusions just in the cycle.

**Amber King:** Exactly and so what your story is it's not uncommon because it has a lot of different effects on where you're starting and kind of the speed at which your counts are recovering. So, a lot of times we have to finagle the cycle where sometime people get extended for a very far time out and they're not on time, but the best part is to make sure that you're kind of in the recovery period adequate enough that we're not dropping your counts down too often to pre-expose you to risk for infection and making sure that you can tolerate the therapy. So, this is kind of a cookie cutter example of what we hopefully if you take a group of people this is a number smack dab in the middle, but by no means is this sort of a checklist that everybody can follow to the tee and your story is a good example of that.

**Q44:** Yeah.

**Q45:** But even though he takes the Vidaza, whenever he does have the bone marrow biopsy it shows no progression in his disease and that's (inaudible 1:51:49). So, he gets his transfusion. Sometimes he questions is the Vidaza working? I'm still getting the transfusions and his doctors in New York had said, well, your bone marrow is the same. When they do take and they see it doesn't show the progression. So, we do have to deal with this, but there's no way of really knowing is it helping or is it not helping because there is no progression.

**Amber King:** Yeah. Dr. Klimek can kind of shed more light on the scenario.

**Q45:** (inaudible 1:52:19)

**Virginia Klimek, MD:** So, this is a difficult (inaudible 1:52:22) but not an uncommon problem and... remember I told you when we look at the blood marrow (inaudible) Vidaza. You can count those blasts (inaudible). When you look at a bone marrow and the main problem is anemia you can't like... you can't look at a bone marrow and expect the treatment to say okay I can see (inaudible) that the cells are (inaudible). There's no visual cues to tell you (inaudible). You need to the counts to tell you. You need to look at the counts at the time and see if your nadir is done (inaudible) low (inaudible) is low (inaudible) transfusion. So, they're giving you the (inaudible) the bone marrow (inaudible). The other thing I want to say and I think this is really important. One of the things that was shown in front of the (inaudible) Vidaza is that even if we don't hang on blast counts, blood counts, even if you don't achieve all of those goals if you can (inaudible)

the MDS... if you can prevent this from going to leukemia, if you can prevent this from getting (inaudible) we know that you can live longer with this disease. You can (inaudible) and so (inaudible) to balance the quality of life (inaudible) you need to balance the quality of life with (inaudible) and you need (inaudible) these injections. The reason it's stable disease may be the best (inaudible) but we know (inaudible) that they can tolerate the drug and (inaudible).

**Q45:** But he also did mention to us that if decides to stop it and (inaudible 1:54:36) Vidaza and say it wasn't working and if he tried to go back he could never start it at the same place... like if he seems stable now it doesn't mean when he goes back to taking the Vidaza that he would remain stable. I don't know if you're understanding what I'm saying. Like you can't just stop it and say let me see how it works. If my numbers drop a lot then I'll just go back on the Vidaza.

**Virginia Klimek, MD:** You can and I (inaudible 1:55:06) if somebody's just getting tired of the schedule or it seems to be wearing them down or (inaudible) for a couple months and they really don't want to (inaudible) we do say okay. Let's see what happens. There's sometimes there's (inaudible) is causing this blood count (inaudible) and then you can maybe get a sense of how your bone marrow (inaudible) sometimes we do that (inaudible).

**Q45:** He didn't want us to do that.

**Amber King:** Moving on. We'll talk about the immunomodulator that we use most often, Lenalidomide which we explained earlier is kind of for a certain subset of MDS and it helps the immune system kind of fight the MDS and it most notably improves the anemia or red blood cell counts. So, the immunomodulator Revlimid that we use most often is pictured before you. So, it's an oral capsule and it's usually given continuously. So, the cycle instead of having a few days on of drug, you just take it every day kind of like a blood pressure medication or a cholesterol medication and there's sometimes that people's other counts kind of go too low we can give people a break within the cycle and sometimes it takes three weeks of active medication and have a week break and it depends on kind of when you work with your doctor and sort of your numbers how you like the medication. It's taken with food or without food, with water, and people take it at the same time every day just to make sure we keep everything at a baseline so we can follow the numbers and results. One thing to note is that if a family member is actually administering the drug to you it'd be good if they wear gloves to protect themselves from absorption. If you're taking it yourself it's fine because you're actually having absorption of the medication, but if someone else is handling the pills they should definitely wear gloves especially if it's a female of child bearing age because they'll go through the biggest side effect of this drug which can be birth defects. One other thing that people are surprised with is that this drug is very strictly regulated. So, you can't go and get it at a Walgreens or Rite Aid or CVS. It has to come shipped from a specialty pharmacy after both the patient and the medical team sign a contract about sort of contraceptive methods while on the medication.

So, as I mentioned the immunomodulatory Lenalidomide just like its cousin Thalidomide was used in the '60s, well before I was born and the Billy Joel songs and caused some birth defects and so that's why there's a special contract that both the doctors and the patients sign that they agree to use contraceptive method which include barrier methods such as condoms and then also oral birth control for females of child bearing age. For patients that are older we just have to sign a contract and make sure we kind of verify that they're above the age that they're no longer of child bearing potential. Also for males they have to agree to use barrier methods just in case they get a female of child bearing age pregnant. There is still a risk for birth defect because the drug is excreted in the seminal fluid. In addition to many of the therapies that we used, this can also cause low platelets and white blood cell counts. So, a lot of the times we sometimes have to adjust the dose and hold it for a few days to help the counts recover and then take the steps from there which we may need a lower dose or a dose less often to get the optimal effect of improving the red cell count without knocking the other ones down collaterally.

So, people can endure something called neuropathy which is signified by numbness and tingling in the toes after a long time on the medication. There are sometimes in the getting of the drug people can get diarrhea of loose bowel movements. We can easily treat that with over the counter agents such as Imodium. There's a very rare incidents of rashes. So, when people first start the medication we kind of have them take a look at their skin and let us know if anything's going on just so that we know if they're allergic to the medication or not and then finally if you read the package information it says there's a risk of blood counts. Now, this medication is actually used a lot in a different type of cancer called multiple myeloma and those patients use a totally different dose and with other medications and they are really at the highest risk for blood clots. So, when we use this medication in MDS, there is a risk, but it's extremely small. So, that's kind of something you'll see on the packing information and your team will talk to you about if they want to start talk about starting this medication.

Any questions about Revlimid or any of the immunomodulators? Yes.

**Q46:** Could you... would a doctor (inaudible 1:59:43) with Vidaza (inaudible)

**Amber King:** So, routinely this is for a special subset that have that deletion 5Q alone and so usually it's used by itself. Now, there are many trials in which we've tried different things, but routinely we usually use Revlimid, Lenalidomide as a standalone agent so that if you can look and see some of the side effects overlap, but I'll just kind of ask Dr. Klimek of her opinion, but usually this drug is used alone, but there's other scenarios for different patients.

**Virginia Klimek, MD:** I just know when given in combination with the (inaudible 2:00:22) Vidaza with Lenalidomide and (inaudible) at higher (inaudible) alone, but then in a subsequent study (inaudible) with Vidaza alone. There was no difference (inaudible) outside of the potential for (inaudible).

**Amber King:** Okay?

Next, we'll talk briefly about the immunosuppressant because considering with the advent of Vidaza and Azacitidine these are honestly not used very often in practice and can have significant side effects and so I'll mention the immunosuppressant are used in select cases when the MDS may be secondary to our immune system overreacting and so the immunosuppressant on the left you'll see there's something called ATGN or anti-thymocyte globulin. So, this is only given IV and so the way we make these products are derived from animals, rabbits and horses. So the biggest side effect and biggest issue are infusion and allergic reactions. So, if a patient starts in a (inaudible 2:01:35) they have to be admitted to the hospital to get the IV over a course daily of four to five days and it's given extremely slowly to ease the body into the medication because there's a high risk for both reactions to the infusion such as shaking, (inaudible 2:01:50) and chills and allergic reaction because these are made from animal products essentially. On the right taking a converse course is something called cyclosporine which you may have heard is used in a variety of different diseases like organ transplants and such and it's an oral immunosuppressant. It's usually given twice a day and the dose is based on your weight and the amount of level of exposure to drug into your body. So, when people start this we have to have them come back frequently to check the levels. If it goes too high which is easy to do with this medication it can be extremely toxic and I'll touch on the side effects in the next study. This drug interacts with a lot of medications. So, it's important if you start this medication or if your family member starts this medication have a nice running list of the over the counter, herbal and prescription medications because any change in your medications could significantly expose or increase your exposure to this drug and cause a lot of bad side effects and then finally as far as dietary considerations, grapefruit juice, pomegranate juice and blood orange juice actually significantly boost the amount of this drug in your body. So, it's important to kind of be aware of those dietary things that you or your family member is starting the drug.

So, some of the notable side effects for both ATG and cyclosporine. It's an immune suppression. So, there is an extreme risk for low blood counts and infection. Kind of (inaudible) amount unique side effects like I mentioned before the ATGAN is from horses and rabbit protein and so there's a high risk for allergic reaction, rashes and infusion reaction. Cyclosporine and among in addition to infection and low blood counts there's a risk for high blood pressure, increased cholesterol, issues with the kidneys, overgrowth of the gum tissue, hair growth and not the good hair growth, kind of unwanted hair growth and then muscle cramping.

So, next I'll touch briefly on herbal medications and supplements. So, one of the biggest questions we get in clinic are what can I use to boost my immune system or I read this online can I take this? And so like Dr. Klimek was explaining before a lot of these medications I spoke before have gone through rigorous clinical trials. We have patients that we have. We monitor, we get tests for, we control against placebos just to make sure they work. Unfortunately, herbal medications don't have the manpower to do that. So, we can't safely routinely recommend



something as we do with medications because we just don't have the evidence that it's safe to use in MDS patients, that it works and then most importantly it won't cause you harm.

So, I'll kind of go over a lot of the stuff that patients ask me in clinic to see if they're okay and like I mentioned before this list is not all inclusive. So, the best thing is that if you go to your appointment and you find something and say hey, I'm starting this. Is this okay? And we were able to tell you yes or no.

So, overall most multivitamins are okay. One thing to check is the iron content. There's a certain group of MDS patients that are getting a lot of iron transfusions. We have to keep a good hold on how much ferritin and iron exposure that they have. So, make a note of how much iron is in your multivitamin and write it down and let your provider know.

Yes?

**Q47:** (inaudible 2:04:59 – 2:05:04)

**Amber King:** Sure.

**Q47:** (inaudible 2:05:05)

**Amber King:** So, there's really nothing that... I'll go through kind of the positive and negative effects, but overall there's no herbal supplement that we know safely and reliably increases platelet count. We've known from experiences there's a lot that decrease platelet count and also stops platelets from working or forming as well and increase risk for bleeding. So, I'll certainly touch upon those as I go through and so some multivitamins actually have weird herbal ingredients in them that actually I'll explain on the next slides can block the processing of prescription drugs and chemotherapy. So, the best thing to do is take a picture of the label and kind of bring it to your appointment and say hey, I'm taking this (inaudible 2:05:47) supplement. I just want to make sure it's okay and it's not causing any harm and then we'll take a look at it and make sure all the ingredients are okay.

Vitamin B we actually prescribe sometimes certain types of anemia and for the most part those are routinely safe and okay. Vitamin B1, B6, B12 and vitamin B complexes routinely don't have many issues and are safe to take. Vitamin D is often prescribed by a lot of PCPs or internists because a lot of us are low and most vitamin D supplements are a-okay. People take 2,000 to 5,000 units a day with no significant impact on the blood counts or overall adverse effects on your MDS therapy. Vitamin A overall is purported or sold to be as an antioxidant TO have these kind of wishy-washy benefits on boosting the immune system. Overall, it's not harmful as long as it's limited to about 3,000 international units a day. After you get doses past this high there's a risk for IT hindering or hurting the liver and so if people are taking vitamin A we don't recommend overall overly endorse it, but we say it's safe to take as long as you limit it to about



3,000 units a day. People often take vitamin C supplements because that does have some benefit to improve the immune system, but it's cautious to be... make sure you limit it to 500 milligrams per day. It is a water soluble vitamin and it goes through your kidneys. So, people with kidney issues actually have a slower time processing a lot of vitamin C and sometimes can lead to kidney stones if you take really high doses such as 3,000 plus milligrams per day.

Yes? Hi.

**Q48:** Is 1,000 too much?

**Amber King:** A thousand. So, there's a line of diminishing returns where kind of taking more is not better and can be harmful. So, 500 is sort of the magic number but 1,000 is in the place where it's okay, but 500 is kind of... that's where the most evidence is and taking 1,000 will if anything kind of put you at more risk for developing kidney stones and other problems. So, 500 or 250 is usually the recommended limit if you would like to take vitamin C. Okay.

And the last thing which is for usually for high triglycerides FOR a portion of the cholesterol panel is fish oil. So, fish oil can affect how well your platelets can form and so if you take a lot of fish oil like over 3,000 of those omega capsules it usually can lead to dysfunction in your platelets and predispose you at risk for bruising and bleeding. So, in patients who have really low platelet counts usually less than 50 our practice is to usually recommend holding off on the fish oil because the risk of you causing bruising and bleeding since you have so few platelets to actually cause clots is very high. So, if you have low platelet counts and you're on fish oil it may be worth a discussion with your local MDS doctor to say that hey, I'm on fish oil. What do you think of my risk of bruising and bleeding because after your platelets get to a certain point the fish oil definitely prevents them from working as well.

Any questions on these so far? These are just the vitamins and supplements.

So, next we'll talk about herbal supplements. So, overall always check with your medical team. The best thing is that we always like to have an open discussion and we like to know what you're taking. When we look at your numbers we like to address all factors that could cause changes assessing both benefit or if something's not working we want to know why. So, whenever you come into clinic and you read something online or your next door neighbor picked up something and said, hey, this works wonders you should try it just run it by your medical team and we'll tell you a) if we think there's good evidence behind it and b) if it's harmful or not for you to take it. Many medications which people don't realize actually interact with prescription medications especially when they're in the extract or supplement form because essentially that's how drugs are made. We take something natural and we concentrate it and put it into a pill. So, all of these herbal medications they sell over the counter actually have drug properties that block other metabolism or prescription drugs that you're taking and overall like we talked about before in the majority of cases herbals don't have power studies to prove that they overwhelmingly have a

benefit to improve blood counts or overall disease. So, that's why we routinely don't have enough evidence to safely recommend them.

So, I have a little warning here is that all of these dietary intake like vegetable smoothies and such don't have these same effects. This slide pertains to when you take like pills, dietary extract forms. So, these are a list of the ones we've been asked by our patients, but certainly it's not all inclusive to all the herbal medications that are sort of out there on the Internet. So, first there's turmeric or curcumin. So, this kind of is sold as an antioxidant magic wonder herbal medication, but it actually inhibits a big liver enzyme that is responsible for processing breaking down a lot of important prescription drugs. The enzyme is called 3A4 which is something you might have heard of, but it blocks the enzyme and can increase your risk for toxicity of other medications if you're taking turmeric supplements and extracts and you're on other medications. In addition, it also reduces how well your platelets are formed. So, just like the fish oil it can increase your risk of bruising or bleeding and especially if your counts are already low this can put you at an especially dangerous risk. The next is milk thistle which is supposed to help kind of improve liver function, but it actually also inhibits liver enzyme that processes drugs increasing you at risk for other drug toxicity. Something called dandelion root, patients like to experiment and try with actually causes low blood sugar. Now, people are already on diabetes medications with low blood sugar know that's a big risk and adding an herbal supplement that's really not shown to have any good benefit could be dangerous and put you at risk for really low blood sugar and it also blocks liver enzymes that processes many drugs and finally a cinnamon supplement has liver blocking properties, low blood sugar properties and blood thinning properties. So, you can see how you pick these up and innocently think it's cinnamon. What's the harm? But when they're concentrated and put into extract these can actually have dangerous properties.

And finally I have one more slide kind of focusing on bleeding risk because considering a lot of MDS patients can have low counts we warn them against routinely taking certain supplements. So, out of the three Gs which all tend to cause bruising and bleeding and that's garlic supplements, ginger supplements and ginkgo balboa. So, these all affect how well the platelets can form and protect you against prolonged bleeding events and so I routinely don't recommend people taking those especially if they have low counts already. The next few like I talked about before, cinnamon and turmeric also increase bleeding risk, also something called papain or papaya extract actually literally breaks down proteins in the body and one of them is an important building block in platelet making and then finally feverfew and fenugreek has been reported to increase bruising and bleeding in healthy patients. So, compound that risk in someone who already has risk with low blood counts it could be pretty dangerous and like I mentioned before these are oral supplements that you can buy that come in a bottle essentially and not dietary or food intake. So, I'm not cutting anybody off of chicken masala or anything like that. It's just oral supplements.

Yes?

**Q49:** Do they comment on the green tea:

**Amber King:** So, green tea as a supplement or drink is okay, but green tea capsules also have a similar property where they block important liver enzymes and so it's important to kind of have a list of prescription medications because there's a lot of drugs that are going to interact.

**Q50:** (inaudible 2:13:25 – 2:13:32)

**Amber King:** Exactly.

**Q50:** (inaudible 2:13:34)

**Amber King:** Exactly. So, a lot of these things aren't really regulated by anybody. I can take one more question and then we have to move on. Yes?

**Q51:** How about foods have any impact on platelets a little bit? (inaudible 2:13:48)

**Amber King:** Oh, foods that may lower it.

**Q51:** (inaudible 2:13:53)

**Amber King:** So for the most part just dietary and food intake. It goes through so many processes and breaking down in your body likely any levels of things that any of these byproducts or dietary byproducts are broken down to the point where they're not dangerous. So, foods for the most part there's nothing we know of that will significantly decrease your platelets and like food products.

**Q51:** (inaudible 2:14:15) same theory?

**Amber King:** Same theory where we don't really have any foods that... that would be great if we had like a magic sandwich that increases your platelet count. We'd offer that to everyone, but unfortunately...

Okay.

**Q52:** (inaudible 2:14:24)

**Amber King:** Okay. Sure. Alright. Thanks, guys.

**Q53:** Thank you.

(Applause)