

Speakers

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(General chat 0:00 – 25:33)

Emily Knight: I want to welcome everyone on behalf of the MDS Foundation to this patient-caregiver forum. At any point if you need to get up, feel free. The restrooms, the men's is on this side, women's is on that side just out the door. Dr. Deol will start with his presentation and we'll go from there. It is going to be... the audio is being recorded and will be available on the MDS Foundation website. So if you have questions, there's microphones or just speak up and we'll be happy to answer anything.

Dr. Deol: I would like to thank you to come out today on a Saturday morning for this session and I'd like to thank the MDS Foundation for organizing this so that we have a chance to interact and go over Myelodysplastic Syndrome. What I'm going to do in my presentation is I'll briefly go over the diagnosis of MDS, how we classify MDS and what are the treatment options that we have available at this time and where things are going in the future. There's a lot of research that is going on in this field to try to figure out what more we can do and how we can do it better so that we can provide better care for patients and try to overcome this disease which in... it's causing issues. As our patient population ages, there's more people who get diagnosed with disease since it's a disease that is generally seen in the older population. So, let's get started.

So basically, just to start off with the basics, the name, the Myelodysplastic Syndrome. It's named because myelo, it's a Greek word for marrow. Dysplasia means when there's an abnormal development of the cells inside the marrow and syndrome is just a group of symptoms that characterizes a disease or illness. So, MDS even though it's one disease, there's different manifestations that it can cause. There's slightly different treatment options based on what we diagnose and what kind of Myelodysplastic Syndrome is. There's a few different varieties of Myelodysplastic Syndrome that are treated slightly different compared to the others. So, it's an important thing to understand that even though this is grouped into one disease, the treatment plan needs to be individualized for individual patients based on what is going on with their disease and what are the symptoms that are being caused by the disease.

So, marrow is where the components of circulating blood are produced from the stem cells. So, stem cells, you can think of them as the building blocks inside the bone marrow that's a factory where all the components of blood are made and stem cells inherently can regenerate themselves and also give rise to cells which can develop into the components that we see in the blood. So, the main components in blood that we see are the red blood cells. So, if there's a problem with red blood cell production, red blood cells help you carry oxygen and if there's any problems with production of red blood cells, the way people present is with anemia, with tiredness, fatigue, etc. The other important cell is the white blood cells which help fight off infections. So if there's an abnormal production of white blood cells, patients might be more prone to get infections. Platelets help you clot. So, these are the main three cells that we have in the blood, the red blood cells, white blood cells and the platelets. So, the platelets if they're deficient, people have

problems with coagulation. They have problems with easy bleeding, bruising. If they have minor cuts they might bleed from them. They might have nose bleeds, gum bleeds, those kinds of symptoms are the things that people can present with.

Usually, the clinical presentation of Myelodysplastic Syndrome is based on what type of what cell line is affected. So if the blood cell line is affected, mainly if patients presents with symptoms of anemia which can cause fatigue, weakness, shortness of breath with exertion, dizziness, palpitations and other things. Leucopenia, that's reduced white cells. People who have reduced white cells are more prone to get infections because their immune symptom is compromised because of the white cells being low. The thrombocytopenia causes bleeding and bruising. So again, people when they present with this disease could present one is because of easy bleeding or bruising from minor cuts. Some people even get to the point that because of bleeding from the GI tract they might have slight oozing in their GI tract which they haven't been able to recognize and that goes on for a period of time. It can lead to anemia, but the underlying feature might be the problem with the platelet production that causes them to have a hard time in terms of clotting and there are people who are asymptomatic and we do see patients from time to time who were diagnosed just because they went for the annual physical exam. Their doctors did their blood work and told them that their counts were low and that leads to further workup in terms of what's going on and they might not have any symptoms from the disease. It might be at an earlier stage that might have caught of the disease might progress down the road to the point that it might cause symptoms. So again, that's... it's very important to make sure that you're having your annual physical exams not only to maintain a relationship with your physician so that they can check and make sure you're not having any symptoms, but also the annual blood work that might be able to... because sometimes we have patients who come in and they're profoundly cytopenic as in their blood counts are low and they haven't been the doctor in many years. So, we don't know how long or what the progress of the disease is. Sometimes it's easier to get a sense if their blood counts were absolutely normal a year before and now they're presenting with very low blood counts. That means within the last year things have gotten progressively worse than over a short period of time compared to if this was something they had lower counts starting off two or three years and slowly they're coming down. It gives an idea in terms of how the blood counts are being affected and that could help the physician and the patient decide on what treatment options would be best based on progress of the disease.

The incidence of this disease in the US is about 4 per 100,000 and approximately anywhere from 10,- to 12,000 people every year are diagnosed with Myelodysplastic Syndrome and with the demographics of our country's population with the aging population there is a worry that we will be seeing more of Myelodysplastic Syndrome because as you see here the median age of diagnosis is around 70 years. So, it is uncommon for Myelodysplastic Syndrome to be diagnosed in young patients, but it's not unheard of. Usually, patients are in their 60s or 70s, sixth or seventh decade is more common time when people are diagnosed with disease, but we've had patient as young as 30s – 40s who've been diagnosed. There are some forms of Myelodysplastic Syndrome that even diagnosed in children. They have certain abnormalities with the repair mechanism of their DNA that predisposes them to get problems with the hematopoietic stem cell and leads to problems with Myelodysplastic Syndrome early in their life, but as a rule this is a disease that we see in mainly in the sixth and the seventh decade of life and the other thing is in the States, we have good medical care and people are living longer. So as you get further and

further in your life, the stem cell pool in your marrow when it's divided multiple times there's risk that it might be getting some genetic mutations every time it undergoes cycle division and stuff and that's the thought that why we see it more in patients in their sixth and seventh or eighth decade of life compared to younger patients.

So, there's no specific causative agent for this disease that has been identified so far like if you think about lung cancer, we all know that smoking does predispose everybody who smokes is predisposed to get lung cancer and there's a higher likelihood of getting lung cancer in those patients, but for Myelodysplastic Syndrome, we still haven't been able to identify a particular causative agent that we can say people... all of the people who get exposed to this agent will have a higher risk of getting Myelodysplastic Syndrome. It is by rule not a familial disease. There are rare exceptions when we've seen in families, but as a general rule most of the patients in Myelodysplastic Syndrome, it's not something they get... they inherent from their parents or they going to pass on to their children. It's a disease we still don't have a good understanding why some people get it and some people don't and we're working on trying to figure out what the causative agents are or what are the things that we can do to make sure that people don't get this disease. Are we able to find early enough that we can offer better treatments for this disease? This is not something that's transmittable. There's no risk of transmitting Myelodysplastic Syndrome. It's not nothing (inaudible 34:46) or any other infectious agents that have been implicated in Myelodysplastic Syndrome that can be transferred from person to person, but there is some risk now that we have had patients who we cure with chemotherapy and radiation for other types of cancers. When your stem cells have been exposed to chemotherapy and radiation there is a risk of damage to the stem cell population and we have seen breast cancer survivors, long term breast cancer survivors, develop Myelodysplastic Syndrome. Patients with Hodgkin's disease who've been treated with chemotherapy and radiation go on to develop Myelodysplastic Syndrome. So, anybody who's gone through chemotherapy there is a slightly increased risk that they might develop Myelodysplastic Syndrome because of the damage that they have, but again that's not to say that chemotherapy is the wrong choice for treating whatever the cancer is at the time when it's diagnosed, but that is something that the physician who's following the patients needs to keep in mind if the patients start presenting with lower blood counts and stuff. That will be one of the things that should start off investigations to figure out if there's any evidence of Myelodysplastic Syndrome.

So, the third diagnosis. What do we need to do? So, we need to do a complete blood count so that basically it gives us all components of blood whether the hemoglobin is low or not, what size the red blood cells are and those help as hematologists figure out whether the picture is consistent with somebody who might be developing Myelodysplastic Syndrome or already has Myelodysplastic Syndrome. It gives us the platelet counts. It gives us the white cell count and also the breakdown of the different types of white blood cells as given in a complete blood count and that helps determine and prognosticate where the counts are, helps us determine how urgently treatment is needed or whether treatment is needed or not. It can help us give some information to patients in terms of what the expectancy is with this type of disease, what would happen in the future and what we can do to try to fight it.

Peripheral blood smear is another important thing that we need to review. We do review patients' blood smears so when they have a complete blood count, a smear is made and when you look at

it under the microscope there are characteristic findings that we see in Myelodysplastic Syndrome patients. Just to name a few, we usually in Myelodysplastic Syndrome the red blood cells are larger than what they would be normally if they don't have... if people don't have any nutritional deficiencies. There's some characteristic cells that we see in Myelodysplastic Syndrome, so looking at the peripheral smear, the hematologist when they look at the peripheral smear can get a sense or at least if somebody presents with low blood counts looking at the peripheral smear gives an idea of whether things might be consistent with Myelodysplastic Syndrome and further investigation is needed in that regard.

The most important test to figure out and diagnose Myelodysplastic Syndrome is a bone marrow expression biopsy and what we do in a bone marrow expression biopsy, it's an outpatient procedure. It's not something that people have to be admitted. Most often than not we're able to do it with local anesthesia like the medication that dentist uses when they work on your teeth. Be able to numb up the skin, numb up the bone and get a piece of the bone marrow and it gives us a lot of information in terms of what's going on because that's as we talked about earlier, it's a factory where everything is being made and we have the end product that we know from the peripheral blood counts that there's something wrong with the end product and we can go and figure out what's going on with the marrow. It gives us a picture, a clearer picture, in terms of what is happening with the marrow and what we also like to do when we do a bone marrow biopsy is also aspirate some marrow into a syringe that can be sent off for cytogenetic analysis and that gives us an idea if there's any chromosomal abnormalities. So, the chromosomes are the genetic material in the cell and if there's any chromosomal abnormalities that will help us prognosticate in terms of their some high risk features, some sorts of Myelodysplastic Syndrome especially with 5Q deletion which we... if we find based on the clinical picture and confirm it with a bone marrow biopsy those can be treated and respond very well compared to other types of Myelodysplastic Syndrome. So, this is one of the most important tests that we have in our arsenal to figure out what is going on and like right now there's a lot of research going on in terms of further prognosticating because we'll go over the classification system of Myelodysplastic Syndrome in a few minutes, but those are whatever numbers you see are median numbers. So, there are people who do better than that and people who do worse than what their prognostic staging indicates and we're trying to figure out why there are some people in that low risk category who might do very well compared to some people in the low risk category who don't do as well and their blood counts don't do as well and the way researchers and scientists are trying to figure that out is to do genetic testing and they're looking at specific genes. So, the chromosomes give us an idea of if there's a big change in the chromosome whereas the genetic testing looks at specific genes and see if the functions are up regulated or down regulated and hopefully in the future will give us better sense in terms of being able to prognosticate what is going on with Myelodysplastic Syndrome on individual patients.

The other important thing always is based on the blood count and peripheral blood smear. There are some nutritional deficiency states that can present with abnormal looking cells. So, that is another thing if based on the peripheral blood smear, the hematologist thinks there's something in terms of a nutrition deficiency that could explain the findings on the blood fill, then the next thing to do is to also check for the nutrition deficiencies, make sure the nutrition deficiencies have been taken care of common ones being B12 deficiency, folic acid deficiency, iron deficiency which can cause different types of anemias, some other things that can happen is

copper levels are also checked. Sometimes if copper levels and low dose can cause abnormalities, too.

So, next I don't want to overwhelm you with all this information, but I think it's important to understand why we have different classification systems and what information the classification systems gives the physician so that they can share it with the patient and then come to a conclusion in terms of what the outlook for the disease is and what needs to be done in terms of treatment. So, the first type of classification is the morphological classification. It's basically it's more of the pathologists way of classifying what is going on in the marrow. Morphology means how the cells appear when you look at it under the microscope. So, the old classification... the older classifications of these 2 is the FAB classification. It's the French/American/British classification system and in 2008 the World Health Organization came up with the classification system that's called the WHO Classification System for MDS. Then we have the Prognostic Classification System which is the International Prognostic Scoring System and the Revised International Prognostic Scoring System and then the WPSS. That's based on the WHO classification and it takes into account the different prognostic markers which we'll discuss and comes up with the score and that helps prognosticate that finish is to prognosticate what the expected outcomes might be with that type of disease and then we can classify MDS based on whether it's something that appeared without any risk factors that we knew of or any preceding hematological abnormalities or hematological diseases which is the majority by far. So about 90... 85 to 95 percent of the people who get diagnosed with Myelodysplastic Syndrome are the D normal kind of something that happened without any preceding abnormality or risk factors that can be identified. The secondary MDS is diagnosed in people like we just talked about, people who've had previous exposure to chemotherapy and/or radiation or have had previous hematological malignancies that have been treated either with chemotherapy or sometimes with allogeneic stem cell transplant. So, those types and the reason to differentiate it between those 2 are the secondary types of MDS there's slightly higher risk of progressing to leukemia and we start worrying a little bit more when somebody has secondary MDS even though they might be classified as low risk disease. So, most of the classification in terms of prognosis that we're going to be talking about is the D normal MDS whenever somebody has secondary MDS, you treat it like it's something that's higher risk compared to even though the prognostic scoring system might indicate that this low risk.

So, this is slide showing the French/American/British cooperative group's criteria for Myelodysplastic Syndrome. Again, this is just for your information. Your physicians will have this information when the bone marrow biopsy is done. More commonly now the pathologists are not using the FAB. They're using the WHO classification system to classify what kind of Myelodysplastic Syndrome this is. So, these terms on the side RAS is refractory anemia, refractory anemia with ring sideroblast is the RARS. RAEB is refractory anemia with excess blasts. CMM is chronic myelomonocytic leukemia and then if you look down here it says bone marrow blast percentage is 21 to 30 percent. With the new classification system, anybody who has more than 20 percent blast is classified as an acute myeloid leukemia. So, this is... That's the older classification and that was the reason why there was need for newer classification system. Once WHO changed the definition and we felt that patients who had more than 20 percent blasts tended to behave more like acute myeloid leukemia compared to MDS.

This is the newer system of classification with that WHO came up with. Again if you look at it, some of the terminology is similar. So, we have refractory anemia, we have refractory anemia with ring sideroblasts. We have refractory anemia with multi-lineage dysplasia or unilineage if you look at the top there's unilineage dysplasia. So, unilineage means it's one line of cells that's affected. So, like we talked about this three cell lines or it could be the red cells that are affected, it could be the white cells that are affected or the platelets. So if it's just one line that's affected and when the pathologist looks at it it appears that there's one type of cells that are not developing normally in the marrow, that's refractory cytopenia with unilineage dysplasia. If more than one line is affected, that's when we define it as a refractory cytopenia multi-lineage dysplasia and then if there are blasts that are increased. So, those are the abnormal cells. Those are the cells that we want to keep it at the minimum and we want them to... and when we do a marrow, we want to see a minimum of those cells. That would be the ideal situation, but that helps us classify and gives risk stratification in terms of whether this is more likely to progress to acute leukemia or not and that is usually the underlying what if of the treating physician is. What is the risk of this disease progressing to acute leukemia because that's usually the event that causes... starts causing more trouble than the cytopenias because we can give blood transfusions to help support the RBC population. You can give platelet transfusions so the platelets are low, but if the disease progresses into acute leukemia usually at that point either you sit down and decided whether treatment is something that the patient can tolerate and if they are then they're treated like an acute leukemia patient and that's what we want to prevent when somebody's diagnosed with Myelodysplastic Syndrome if we can get to it in time and hopefully we can prevent the progression to acute leukemia.

And this here just helps us, the next 2 classes, the refractory anemia with excess blasts 1 and 2. The difference in both of these is just the number of blasts that we see in the marrow. So, if it's less than 5 percent blasts, it's RAEB1. If there's anywhere more than five percent blasts, but less than 20 percent that we diagnose AML it's RAEB2. There is overlap syndrome where some myeloproliferative disorders and Myelodysplastic Syndromes kind of overlap. So, that's kind of the unclassifiable Myelodysplastic Syndrome and then if... WHO has created a specific category of myelodysplasia with the 5Q deletion and we'll talk in a few minutes why that is... this a type of disease that patients respond very well to with an older type of chemotherapy agent and a very high percentage of patients will respond to it and their count should normalize and they can do well for many years with the drug that's an older chemotherapy.

So, then based on the pathological diagnosis, the morphological diagnosis, that gives us an idea as to what it looks like, how aggressive it looks under the microscope, but then we went further to figure out what happens to different patients based on all of these things that we think are important. So, things that we look at are how many blasts are in the marrow and, again, if you look at this, this is the older system and we've... and that's why we have the Revised IPSS because this takes into account 21 to 30 percent blasts. At this time if somebody has 20 percent blasts in the marrow, 25 percent blasts in the marrow, they would be classified as an acute leukemia because we have seen that the... Go ahead.

Q1: So, blasts are an abnormal cell. Is that what it is?

Dr. Deol: Blasts are abnormal cells. Those are the cells that are... the leukemic cells or they behave like leukemia cells. We want to... if they get above a certain percentage, we've learned that those patients behave more like acute leukemia than Myelodysplastic Syndrome.

Karyotype means what we just talked about the chromosome changes. Normally, everybody has 46 chromosomes and then the male chromosome, male or female chromosomes in addition to that and if there's any abnormalities in the chromosomes that helps us determine what risk category they come into and then cytopenias means how many blood lines. So, red blood cells affected, white blood cells affected, both are affected, platelets are affected. That helps come up with the score. If you see on the top, there's the scoring system. So you can get these many points based on where you fall in the category and based on this you come up with a scoring system. So the low risk patients are patients who have less than 5 percent blasts, their chromosomes show no abnormal or what is some features on chromosome analysis and they don't have either any cytopenias that... and by cytopenias I mean their hemoglobin should be less than 10. Their neutrophil count, a type of white cell that helps fight off bacterial infections, is less than 1,800 and platelets are less than 100,000. So, those are what we classify as cytopenias. So, they might have slightly lower counts, but not to the point that they have significant cytopenias. Intermediate 1 risk category, you have 1.5 to 1 on this scoring system. Intermediate 2 is 1.5 to 2 and high risk category is 2.5 to 3.5.

And this next slide gives you an idea as to why this important. So if you look at the risk category here based on the age and based on what risk category patients are diagnosed in. This is not a dynamic system. This is a system at the time of diagnosis that you can try to prognosticate what's going to happen in the long run. So if somebody is in the low risk category, the survival is extremely good. You can have years without causing any problems or progressing to leukemia compared to the high risk category when things need to be started. This is in if there's no treatments done. So, what the understanding is these are patients when we did... didn't have treatments. This is what happened to patients if nothing was done for the underlying disease and that helps us determine what needs to be done and how urgently things need to be done. So somebody who is in the low risk category who doesn't have too much trouble, they might have a hemoglobin of 11 or maybe 10.5 and it's not causing too much symptoms, those patients can be observed for a period of time without requiring any treatment compared to patients who might be in the high risk category who have increased blasts in their marrow and have chromosome abnormalities but their blood counts are not much affected. The likelihood is that in the next few weeks to months things are going to get worse and those are the patients that need to be started on treatment. So, it helps the physician and the patient understand where they are in terms of the disease and how aggressive we need to be in terms of starting treatment and that is helpful to come up with an individualized plan for every patient who gets diagnosed. Again, this is the IPSS system... Go ahead.

Q2: Is this a median survival (inaudible 52:37).

Dr. Deol: Median survival. This is without treatment. So, this is the new system that we have. This is the Revised International Prognostic Scoring System like we talked about. Since we've changed the definition of acute leukemia from 30 percent blasts to 20 percent blasts, there was a need to come up with a better system and as we learned more about this disease, we did figure

out that patients who had more problems with cytopenias if you look at it, the last one, the International Prognostic Scoring System then it just said cytopenias 1 or 2 or 2... 0, 1 or 2 or 3. If you look at the new scoring system, it gives us more in terms of where the blood counts are. So if your hemoglobin is more than 10 grams, your platelets are above 100, your neutrophil count is about 800. You come in the low risk category. You get 0 points for that compared to somebody who might have more problems with hemoglobin. Somebody who has their hemoglobin is between 8 and 10 or less than 8, you get more risk and that helps us prognosticate the disease a little bit better and what we see here is the risk category. So if you notice, there's 5 risk categories here compared to 4 that we had previously. There's very low risk category, there's low risk, intermediate, high and very high risk category and, again, if you look at the median overall survival, it kind of follows the pattern that patients with lower risk disease do very well. Patients with intermediate and high risk disease have a higher risk of causing problems. Patients who have very high risk have more issues with progression to leukemia and this is... on this side is the median time to that about a quarter of the patients will progress to leukemia. So if you look at the very low risk category, more than 14 years that about 25 percent of patients will respond... will progress into acute myeloid leukemia and that's the thing that you want to prevent from happening or you don't want it to happen compared to in the very high risk category in about .7 years. So about half, 6 months to 8 months, 25 percent of the people would have progressed into leukemia which is the event that you want to try to prevent if you can.

This next system is the WHO the WPSS classification system and, again, there's lots of classification systems, but the take home point from all of this is whatever system your treating physician is using it gives them a sense in terms there's not a whole lot difference in terms of if you're a low risk or a very low risk category that means the chances of disease progressing to leukemia and causing problems is low. If you're in the high risk it's high. So all of these prognostic systems just put in the data that we've figured out so far is important in terms of prognostication and gives us that information so that we can come with an individual's plan and it doesn't really matter a whole lot which type of classification system your treating physician is using as long as you and them have come to an understanding this is where we are with the disease and this is what the expectation is. This is what we need to do to try to prevent progression to leukemia and, again, this is again going back, we classify it based on the WHO risk category. So, those different classes that we saw based on how the pathologist looks at it and sees what they see under the microscope. So it gives you different points for those categories, what your chromosomal abnormalities are, whether there is transfusion requirements as in people who requiring blood transfusions, platelet transfusions, to help support them. That gives them more points and based on the points, they come up with 5 risk categories in this classification system, too, and these are just the graphs to show what the median survivals are. So if you look at the 50 percent mark that would be the point that you would look for survival of median survival. So again, by median survival I mean there'll be patients even in the low risk category who might have progression of the disease quickly. So, it's important that the physician is keeping an eye out what's happening because there are patients with low risk category who can progress to leukemia too and this is a median in terms of where we expect half the people to have progressed or half the people to have had some complication from the disease and unfortunately it is hard to put it on 1 individual person like if I have the disease, I don't know what's going to happen to my disease even though I am in the low risk category. It's time that's going to determine how quickly or how slowly my disease progresses. So, it's important to make sure that

you're following up and keeping a close eye with your hematologist on what's happening even though you might be in the low risk category.

So, treatment caveats. Not all patients who get diagnosed with MDS will require treatment right away. It's not something like if you're diagnosed with a low risk disease you don't have any significant cytopenias that are requiring... that are causing problems and symptoms with bleeding or infections or problems with fatigue and tiredness. There are patients that we find out on blood work that they've had for a few years their counts have been low and they're low but stable for many years that we go back and get their reports from previous times that they've had blood counts checked and there are patients that we observe for a period of time and they can do well for long periods of time without requiring any treatment, but again like I said it's individualized treatment for every patient and more information you have in terms of what the Prognostic Scoring System where you fall in that category that helps you and the hematologist come to a conclusion as to what would be the appropriate treatment options for that kind of disease.

The only curative therapy... We've done a lot of research. We've had drugs and we'll talk in a few minutes about what drugs we have, but the only curative therapy that we can say that people can be cured of in Myelodysplastic Syndrome is a stem cell transplant. So, with all the chemotherapies and all the drugs that we have, we can control the disease for a period of time, but eventually it might have problems. It might progress into leukemia or people might stop responding to treatment at some point. So, that's to keep in back of your mind that if cure is a treatment based on the discussion with the physician and we'll talk about what stem cell transplant involves in a minute, but that is something I think there are people who might not have been evaluated by a transplant physician. I think it makes sense to, not for everybody, but if there are no significant co-morbid conditions, the people are otherwise in good health, I think a discussion with the transplant physician to go over what transplant involves is an option that should be available by more people and I think there needs to be a little bit more awareness in the community with the physician that we've come a long way in the last few years in terms of how we take care of transplant patients with different transplant regimens and there are more and more people who we can take to transplant because of newer stem cell sources that we're able to utilize.

So, these are just a slide briefly looking at what treatments we have available at this time for patients with Myelodysplastic Syndrome. So if you look on the left side of your screen, the 2 approved chemotherapy agents for Myelodysplastic Syndrome that can be used in any type of Myelodysplastic Syndrome is Azacitidine and Decitabine. These are if you can call them similar drugs. They're cousins, if you will, which work with a similar mechanism of action. The thought is for some people there is a hyper (inaudible 1:00:45). There are some genes that are turned on and with these drugs we can suppress those genes and patients can respond. So, these are the 2 drugs that have been approved, Azacitidine and Decitabine. Revlimid is another drug that was initially brought... was investigated for multiple myelo and people with multiple myelo may respond very well to this drug and we found out that for a certain type of Myelodysplastic Syndrome especially patients who have the 5Q deletion, this drug works very well. About 60 to 70 percent of the people with the 5Q deletion will respond to this drug and have a good response that can last for a long time with this drug. There are studies where we've looked at Revlimid in

patients who don't have 5Q deletion and there's a small response in those patients. About 20 percent of those people who don't have 5Q deletion might also respond to Revlimid, but it's not approved... it's not a FDA approved indication for Revlimid to... for patients who have Myelodysplastic Syndrome other than 5Q deletion. The other problem that we run into with patients with Myelodysplastic Syndrome is if they become transfusion dependent as in their having symptoms from their anemia and they're getting transfusions regularly. It comes to a point that every time you get a unit of blood, you get some extra iron into your body and over a period of time that starts accumulating in your body and can cause problems with inflammation of the liver and other problems. So, there are approved agents that can help get rid of the extra iron in your body and usually when people have had about close to 20 transfusions of red blood cells that's when you start worrying about excess iron in your body and start thinking about... the physician will start thinking about using some agents to try to get rid of some of that extra iron, so that doesn't accumulate in the liver and start causing problems there.

On the right side of your screen, these are growth factors that are approved for other indications but we have found some use for them in Myelodysplastic Syndrome. These are the red blood cells. So like we talked about, there's three types of cells, the red blood cells, the white blood cells and the platelets and we have agents that we've been able to come up with that help stimulate growth of each types of cells. So, it'll stimulate the bone marrow cells to produce more of one or the other type of cells and for the red blood cells, there's two agents called Epoietin and Darbepoetin which use for patients who have problems with low blood counts and have lowered erythropoietin levels. For the white cells, we have three agents that are approved right now that can help stimulate white cell growth. These are not approved for use in Myelodysplastic Syndrome, but we have experience and there are certain situations in which we've used combinations of erythropoietin stimulating agents along with white cell stimulating agents and we've seen a response in patients. The newest of these are the platelet growth factors that are coming out. There's two approved platelet growth factors right now for use in patients who have immune thrombocytopenia or a destruction of their platelets and there's been some research that's been going on into using those agents in Myelodysplastic Syndrome and we'll talk about them briefly as we go further down the talk. For a certain type of Myelodysplastic Syndrome when we look at the marrow it appears that there's very few cells there. Usually if you think of your marrow being a factory, it's trying to produce everything that's in the blood. If there's a shortage with the inherent systems in your body, your bone marrow gets stimulated to make more cells even though it's not developing normally. So usually when the marrow is done, we see lots of cells, but they're not developing normally, but in certain types of Myelodysplastic Syndrome we see a paucity of cells that there's very few cells in the bone marrow and for those patients we think they might be a problem with immune destruction. The immune system for some reason is destroying some of the precursor cells in the marrow and sometimes immune suppressive therapy in those situations might be the answer and that patients can respond to immune suppressive therapy.

There are other agents like thalidomide androgens which have been used to help stimulate the marrow and maybe have some more production of especially the red cells where the androgens that usually increases the production of red cells and sometimes platelets to help somebody who is transfusion dependent maybe become transfusion independent for a period of time, but, again, these are not approved indications for these drugs and it's very specific for who gets these drugs

and whether they're able to respond. It's a decision that's made by the treating physician based on an individual patient at that point and then stem cell transplant like we talked about is another indication... is another strategy that we have to potentially cure Myelodysplastic Syndrome. So, did you have any question? Did you have a question?

So, we'll go over the treatment options like we talked about. So treatment options could vary from observation or supportive care based on what symptoms the disease is causing all the way to as aggressive as a stem cell transplant which we'll talk about what that involves and in the middle, there are some other strategies that we can use to alleviate the symptoms and maybe get a response for a period of time with the understanding that eventually at some point the disease might progress despite use of these agents. So, the other agents are the growth factors. There's immune modulation that's available with the Revlimid or immune modulation with the immune suppressive therapy for certain types of Myelodysplastic Syndrome and then the chemotherapy. So, I'll try to finish up quickly so that we have some time for some questions.

So for supportive care, basically what the goals of therapy are is to make sure that we are taking care of the symptoms that the disease is causing. So, the things that are... we can support with transfusion is mainly for red blood cells, you can get red blood cell transfusions that people who get symptomatic with shortness of breath. Some people have underlying heart disease that they start feeling more short of breath or have chest pains and stuff when their hemoglobin falls below a certain level. For those patients, we have to make sure that we individualize the plan. There are some people who even at hemoglobin of 10 will have a lot of symptoms. There are other patients who are in good physical condition who may be at 8 or 7 grams of hemoglobin are walking around without any symptoms. There's no magic number that you have to achieve to keep it. It's (inaudible 1:07:41) based. If somebody's being supported with transfusions, it's mainly based on what symptoms the disease is causing and then managing it appropriately and that helps prevent iron overload. So if somebody who can tolerate a hemoglobin of 7 or 8 and gets transfused every time they're below 10, eventually they're going to get iron overloaded. So if you can try to prevent that that's a strategy that we utilize more often and individualize it based on the symptoms that patients are having and most of the patients will be able to tell us this is the number when I get around here is when I start feeling that I need a transfusion. I'm more tired and more fatigued and I'm not able to do stuff and we can figure out that threshold for individual patients and try to keep them above that.

Platelet transfusion is another way to support platelets if patients are having problems with bleeding. That's when we can support them with platelet transfusions. However for most of the patients with Myelodysplastic Syndrome, we don't try to prophylactic them to prevent bleeding because usually this is a disease if we are just doing supportive care, that's a disease that we probably are not going to be able to cure and over a period of time platelet transfusions might become ineffective because you start making antibodies to platelet transfusions and more platelet transfusions you have, the higher the likelihood that you'll have antibodies and if and when the patient gets to a point when they might need a surgical procedure or they're having bleeding for some point they might not respond to the platelets if we're just keeping the platelets above a certain number. So most often than not we try to keep platelet transfusions to a minimum and utilize them in case there's bleeding that the patient is having or there's a surgical procedure that they need to get through. Those are the indications for using platelet transfusions. Again, no

magic number that we need to keep the platelets above. Even at platelets of 50,000, people can have major surgeries. So, it's sometimes the surgeons we go back and forth with surgeons. They want platelets at a certain number before they'll do surgery and we have to go back and discuss it with them because there's no magic number. As long as the platelets are working well, even 50,000 platelet count should be appropriate and adequate for a surgical procedure.

The other thing for patients who have problems with infections because of low white cell counts, they can be put on antibiotics to help fight off the infections. Usually again, prophylactic antibiotics are not done routinely until there's lots of infections or you're trying to prevent certain types of infections because of the risk that the bacteria and the viruses and other things when you have them on agents for long period of time without an active infection they can become resistant which you try to save the antibiotics for when there's a true infection and then that's when you use it rather than using prophylactic antibiotics and the transfusions for this if somebody's on supportive care, the body is to make sure that the transfusions are being done at an appropriate level so that we prevent iron overload and if there are indications that somebody is going to require more transfusions that planning on some of those agents that can help remove iron from the body is another talk that the hematologist and the patient should discuss and make sure that they're there, they have a plan for that and usually that number is about 20 transfusions when somebody's had about 20 red blood cell transfusions is when you start worrying about iron overload and starting thinking about therapies to chelate iron from the body.

Growth factors like we talked about can stimulate production of red blood cells, white blood cells and platelets. So right now mainly we use the erythropoietin stimulating agents. So patients who have low risk disease and have a low serum erythropoietin level so that means their body's not producing enough erythropoietin to stimulate the marrow for producing more cells. So, somebody's body's already producing a lot of erythropoietin and their erythropoietin level is really high, adding more erythropoietin from the outside usually doesn't help. So, this is a result for patients whose erythropoietin levels are low despite the anemia and those patients are the ones that might help... might be helped with the erythropoietin stimulating agents and sometimes we add growth factors, the white blood cell growth factors, and they can work synergistically to improve the (inaudible 1:12:12).

The platelet production can also be increased with Thrombopoietin mimetic agents. This is the newest class of drugs that we have and there's more research that needs to be done in this class of drugs to figure out whether we can utilize these drugs in Myelodysplastic Syndrome. There is the chances of response for these agents is in the neighborhood of around 30 to 40 percent. It could be higher, as high as 60 to 70 percent in appropriately selected patients and as low as 10 percent if the patients already have a higher erythropoietin level. There's very low chances that people will respond to the erythropoietin stimulating agents.

The platelet stimulating agents are the drugs that we talked about. They're approved right now for use in patients who have an immune destruction of platelets and we feel in Myelodysplastic Syndrome there's a paucity of production in the marrow. So, the appropriate thought was maybe we should use these agents to stimulate out the marrow so that we can have more platelets come out into the blood. So, one of the agents, Romiplostim, was investigated in a trial to look at Myelodysplastic Syndrome, but this trial had to be stopped early because the slightly increased

incidents of acute leukemia in the group. So, there's patients who were randomized half and half. I think it was 2:1 randomization. So, more people got the investigation agent and few people got the placebo agent or a pill to see what was the difference and in the group that had the Thrombopoietin stimulating agents, there was slightly increased risk of acute leukemia. So whenever we have trials, we have investigators look at the data at various time points to make sure that this is not something that's causing more risk even though theoretically it makes sense to stimulate the platelet production and stuff, but we sometimes can have unintended consequences of medications and because of that this study was stopped early. We're still trying to see if this does time out in the long run or this was something that we just found by chance. So, that would be something that we hopefully in the next few years will learn more as we get this data becomes more mature and we have more data available.

The immune suppressive therapy is used because there's some overlap in other bone marrow failure state called aplastic anemia and Myelodysplasia and some patients with Myelodysplastic Syndrome especially when we look at the marrow under the microscope and it looks that there's very few cells there. Patients who are younger usually 60... below 60, they have a certain type of markers in their stem cells called the HLDR15 and have low risk disease. Those are the patients who have the highest chance of responding to these immunosuppressive therapies and it usually takes weeks to months for somebody to see a response to the immunosuppressive therapies. It's done... There's an antibody against the immune cells, the T cells are the immune cells in the body and there's antibody against that along with the maintenance phase of cyclosporine that goes on for many weeks to see if there's an improvement in blood counts.

Lenalidomide or otherwise better known as Revlimid is a drug that's approved for multiple myeloma and for Myelodysplastic Syndrome with 5Q deletion and like we talked about anywhere from 60 to 70 percent of the patients with this type of disease with 5Q deletion will respond to Revlimid and mostly there's a higher preponderance of females with Myelodysplastic Syndrome who have this deletion. Usually, these are patients who have isolated anemia. Their platelet levels are usually higher. So, those are some of the things that when we see blood counts if it kicks off the thinking in the hematologist's mind if somebody who has just isolated low hemoglobin, platelets are a little bit high there's evidence of Myelodysplastic cells in the bone marrow, there's a higher likelihood that they would have the 5Q deletion. It might be the people who might respond to this drug.

There is a small response rate in patients who have... who don't have this 5Q deletion. So, that's sometimes I've... we've in our practice used it. I've used it once or twice in patients who don't have the 5Q deletion and still patients have had a brief response to this drug. It's much smaller. So, in patients who have 5Q deletion, about 60 or 70 percent of people will respond. People who don't have it, maybe 15 percent of people might respond to this drug. So, that's another treatment option that we have available in our arsenal.

The hypomethylating agents like I talked about, it's we think one of the genes is turned on that causes problems in some patients with Myelodysplastic Syndrome and we're trying to figure out more is whether these are the patients who actually benefit because there are people who don't have those genes turned on and still benefit from Azacitidine and Decitabine. So, these are the two drugs that are front line therapy right now for most patients with Myelodysplastic Syndrome

and usually we need to give a few cycles. You cannot determine by 1 or 2 cycles whether somebody's going to respond or not and people will have... their counts will go lower with these drugs. These drugs do cause problems with lowering of counts before they get better. So, 1 or 2 cycles and counts are lower doesn't mean that it's not working. We usually have to... We plan on giving at least 4 cycles repeating a bone marrow to see if there's an improvement and there are times when it takes up to 4 months to see a response with these drugs and the response rates range anywhere if you look at different studies anywhere from about 35 – 40 percent up to 50 – 55 percent with these drugs and average duration, the median time that people who respond to these drugs are close to about a year or so. So again, it's median time of response. It doesn't mean that everybody... There are people who are on these drugs for years and tend to be well controlled. There are people who might have initial response and might progress really quickly. So again, like I said, we still have ways to go in order to understand better why some people respond, how some people respond, why it lasts longer in some people, why it doesn't last as long in other people.

Allogeneic stem cell transplant is appropriate for selected patients. So, the problem with stem cell transplant is there is a chance of dying from this procedure. So, that's the reason why there's a concern and hesitancy in terms of proceeding with a stem cell transplant, but this is a modality that we have that we can potentially tell patients that will be cured of this disease and might not have to worry about this disease in the long run and the important thing that I want to make sure we address and we're trying to raise awareness in the community is to make sure that people understand there's no age specific cutoff for transplants. Previously when they started doing transplants, 40 was... 40 or 50 was the cutoff for people who could go through stem cell transplant and as we like to joke in our community is as those transplanters got older they moved every time it moved another decade, another decade. So, we have had patients in their seventh decade who've successfully gone through transplant. It is not chronological age that matters for stem cell transplant. It's what the patient has in terms there are people who in their 70s who are healthier than 40 year olds that I've seen in my clinic and those are patients that I would offer a stem cell transplant to compared to somebody who might be younger but has so many other comorbid conditions that the chances of complications from transplant are much higher.

This is just a graph from the CIBMTR. It's one of the organizations that keeps data on all the transplants that have happened. So sibling donors means a brother or sister being a match and there's 25 percent chance that any of your brother or sister will be a match for you. If not then we can look at unrelated donors. There's about 16 million people on the National Marrow Donor Program Registry who we can answer from the computer database to know if somebody's going to be a match for a patient or not. So if you look at it, this is from the last decade, 2000 – 2010. The chances of people being cured. These are patients who are 5 years out, 5 – 6 years from transplant. It's in the neighborhood of around 30 to 45 percent or so patients can be cured of disease even patients who have advanced disease who undergo unrelated donor transplant. So, that is a really good option, but for appropriately selected patients.

So, what do we have in the future? There's lots of drugs that we have. We're working on genetic mutations to further prognosticate patients because like I said even patients with low risk might behave differently. It's hard to put that data from hundreds of people on one individual patient and now we're trying to look at genetic mutations to figure out if we can prognosticate the

disease further and try to figure out which ones even the low risk disease might be the patient that might need treatment early on and might progress early on and there's lots of combinations that are being investigated. Some of the agents that are approved, we're trying to put them together and see if we can improve the response rates. There's lots of novel agents that are being looked at to see as we understand more about the genetic mutations what is happening or where the problem is to try to fix what small molecules that can fix that genetic abnormality. If a gene is turned on, it can turn it off or turn on genes. Though, that's something that's being looked at and we've come a long ways in terms of stem cell transplant. Previously it was transplant was only limited to patients who had a brother or sister who was donor and was available. Now, we have cord blood transplants. We can do transplants from children which we call haplo transplants. So, there's other stem cell donors that are available right now which more and more people are able to find a donor and can proceed to a stem cell transplant if it's appropriate for them.

This is just a slide to show you the different mutations that we are looking at right now and basically these mutations drive different things. So, there's mutations that they drive the (inaudible 1:22:29) as to how populated the marrow looks like there's some mutations that look at how the cells differentiate and develop normally. There are some genes that look at what turns on the development of red cells, white cells, platelets at different points and some other mutations that we have. So, we are looking at these mutations even in patients who might have good risk or low risk disease to figure out if we can prognosticate those patients further to figure out which of those patients might be the ones that might progress earlier or might not do as well as you would expect them to be just based on the IPSS scoring system.

These next few slides are all the drugs. These are three or four slides here. These are all the drugs that are being looked or have been looked at and there are early studies that are being done which looking at Myelodysplastic Syndrome with all of these drugs. Again, that's always a moving target right now with everything that's going on with the funding, resources and stuff. There is a paucity in terms of getting research funding for studies for newer drugs. Usually it's dependent on the company that makes the drug whether they're willing to share that drug even though there might be a theoretical. You find out about a mutation, you know there's a drug available that can help that mutation. We don't have as much funding available through an (inaudible 1:23:55) right now to start a clinical trial just based on that. Usually we have to go to drug companies and see if they're interesting pursuing a clinical trial and then trials happen. So, that's a long process, but there's a lot of dedicated researchers who are working and looking at trying to figure out new targets that we can find that we can treat and cure and hopefully find a cure for this disease and provide better therapy to our patients and these are some of the resources that I just put together. These are some of the websites that you can get some more information, some education material, about MDS and clinicaltrials.gov is a good source to see if there's any trials available in your area. Usually, most of the companies has cancer centers will have some trials that are available for specific diseases and I think contacting those centers to see if there's any trials for Myelodysplastic Syndrome because that's the way we learn. We have come so far is based on patients who decided to participate in clinical trials so that we can take the next step about finding out about a new drug and going forward.

So, this I'd like to end I'll take any questions. Thank you.

Q3: How often do you have to have bone marrow biopsies?

Dr. Deol: So, bone marrow biopsies usually for patients who if they have low risk disease and their counts are stable, I might do it every few months to figure out if there's any change that's going on and other patients if I see indications that their counts are dropping unexpectedly, I would do them more frequently. So again, there's no one time period that affects everybody. It's based on how what kind of disease they have, what their chromosomal abnormalities are and what's happening with their blood counts (inaudible 1:25:46) when they're following them will decide when it's appropriate to do bone marrow biopsies. For patients who are on treatments, say, with Azacitidine or Decitabine, I usually will start them on treatment I know that they're going to have low blood counts with the treatment before the counts get better. So, I usually wait for about four cycles before I repeat the bone marrow biopsy until if there's something that I see in the blood counts that is what is the (inaudible 1:26:09) I can do (inaudible 1:26:10).

Q3: So if you (inaudible 1:26:11) bone marrow biopsy shows that you have the beginning of this but then your counts remain stable normal. We're talking hemoglobin 15 and all this sort of stuff. Is there a need to get any, you know, every month get another bone marrow?

Dr. Deol: No.

Q3: We wait till the number...

Dr. Deol: There's evidence that there's something that's changing.

Q4: Are you familiar with a clinical trial phase two of ACE-011?

Dr. Deol: (Agreement sound) So, it's the older of Azacitidine that's been looked at and there's about anywhere... I think it's about 35 percent in these primary studies have shown about 35 to 40 percent response rate to the AZB, the older Azacitidine and there's some... there's other things that we're looking at is to improve outcomes of transplant, we're looking at using some of these agents post transplant to prevent the disease, the chances of relapse after transplant, too.

Q4: Because it's not... It's being performed throughout the United... Actually, I'm in it the phase in ND Anderson in Houston. The other question is so if you don't respond over a period of time to either Dacogen or Vidaza, what is next? A clinical trial? Is there anything in between?

Dr. Deol: So usually, again, it depends on what's happening in terms of the disease progression who if somebody is not responding and their disease is progressing and they have a donor available and they're in a good enough condition that they can go to a stem cell transplant, that would be an option at that point. Clinical trials always if there's a clinical trial that is appropriate and makes sense. I think that will be the best option.

Q4: For my personal condition, I've had it for 14 years and still in a low risk category, so but I had the opportunity through... We used to live in Texas and we have family down there through ND Anderson to start this trial.

Dr. Deol: The clinical trial.

Q4: Which I just started.

Dr. Deol: That's good. Excellent. And it's because of patients like you that we've come so far with the treatment options that we have.

Q4: One other quick question. There's a difference of opinion when you have ferritin level of 1,000 or 1,500 or... as to when you should or don't need to use Exjade, say?

Dr. Deol: I think my thoughts on that are usually if it's above 1,000 and patients are requiring transfusions there's no way that your body can get rid of that extra iron. So, I think I do... my personal opinion is I support use of chelators when your ferritin level goes up and you've had those transfusions because even for patients who had transplant, we're learning now patients who have a higher ferritin level going into a transplant, they have... that's one of the adverse features that those patients don't do as well with transplant because with all the (inaudible 1:29:06) that the transplant brings along with it if the liver is not in good enough condition, it can get damaged more easily with when we are going through the chemotherapy for the transplant.

Q5: Just a follow up on his thing. I have hemochromatosis along with this here. My ferritin level was 500 when it was diagnosed. I've had 12 – 13 phlebotomies in the last year and a half. So, my ferritin level's now down to 80. I mean, it has to come down. I can't have all that high iron that I've had. So, okay, so the rest of my life I have to have these phlebotomies. So instead of going with this Exjade...

Dr. Deol: You have normal red blood cells that you can tolerate for about taking blood off. Most of the patients run into trouble is because they are transfusion dependent. They're getting blood into their system every few weeks rather than us... and if you try to take blood off... If you can, that's the best and the quickest way of getting rid of extra iron in the body is to take red blood cells out of the body, but for these patients because they're dependent on transfusions we can't do that and then we have to give them agents that help chelate the iron out of the body and they can excrete the iron.

Q5: That's based on ferritin. You know, the Hemochromatosis Society says you should have ferritin levels of 20, but the labs all say oh, it's 20 to 400 is normal. That's baloney. I mean, it's like saying your blood sugar is (inaudible 1:30:29).

Dr. Deol: Because of hemochromatosis your body's metabolism is it tries to accumulate all the iron that your absorption is increased. It's getting extra iron into the body. So for hemochromatosis, even 400 might be a risk factor because the chances of you going higher than 500 and start causing... having trouble and stuff is going to be higher compared to somebody who just because of extra transfusions is getting to 300 or 400. So, there's a difference with the hemochromatosis because you're more prone to accumulating that extra iron and keep it in your body.

Q5: Is there a level where you like to have for hemochromatosis have ferritin (inaudible 1:31:08)?

Dr. Deol: I think below 100. I'm pretty comfortable with that. Questions?

Q5: I don't want to hog the thing here.

Q6: After transplant which is me. Actually, you did my transplant in September. What is the indicator that there is a cure?

Dr. Deol: So basically if the blood counts stabilize. So after transplant, the blood counts can be low for (inaudible 1:31:42). There could be infections. There could be medications that we give to prevent those infections that can cause... It's like (inaudible 1:31:48). As long as the levels we have patients who go into transplant requiring blood transfusions every few weeks, platelets running low and after transfusion the platelets might not go up to normal, but they're at 100 or 120 and they stay steady there and the hemoglobin is maybe 12 or 10, but it stays steady without requiring transfusions. So basically and most of the patients we will do a bone marrow biopsy after transplant to determine whether they're in remission or not and there's no evidence of Myelodysplasia.

Q6: At what point would that first biopsy be after a transplant?

Dr. Deol: It depends on the disease if there's a lot of blasts and then if there's a risk that things are not working, I might do it as early 30 days after a transplant, but routinely we do it close day 100 after transplant to see... to look for remission.

Q6: And then after that it's just based one test.

Dr. Deol: Based on what's happening with blood count because we have ways... we have the donor's DNA, we have the recipients DNA and we can figure out how much of the cells are donor cells and that gives us an idea of whether the marrow is mainly donor cells or whether the recipient cells are coming back and that would be what I'm saying if the blood counts are going low and the donor cell numbers are going down those would be things that you worry about.

Q6: Okay.

Q7: These cell lines you're talking about on the chromosome. I don't know. What are you talking about?

Dr. Deol: The chromosome abnormalities?

Q7: Like you had said a 5Q. I've got a 20Q.

Dr. Deol: Okay. So, 20Q is another indicator. It's a better risk disease that people have. So, it's basically when the chromosomes, you have 2 sets of chromosomes for each of the chromosome. So, what the pathologists do is they take the sample from the bone marrow and grow it under

artificial media and they look at about 20 cells under the microscope to see what's happening with each of the chromosomes and P and Q. P means the short arm of the chromosome. Q means the long arm of the chromosome. If part of it is missing, that how it's... so if 20Q. Is it deletion 20Q that you have?

Q7: Yeah. I have... So I have normal cell line in 9 and 20 cells with chromosome 20Q deletion.

Dr. Deol: So, it's the long arm of chromosome 20 that's missing in 9 out of 20 cells. They look at about 20 cells to give an idea of how many abnormal chromosomes are there. So in about 9 of those 20 cells, you have an abnormal chromosome.

Q8: Would you please explain the process for a stem cell transplant from the beginning, the very, very beginning?

Dr. Deol: Sure. So, for what a stem cell transplant usually when you have patients come in who are diagnosed with disease or have been started on treatment, the first thing we do is we sit down and assess what the medical condition is for the patient whether it's appropriate and whether their organ function will be adequate to go through a stem cell transplant or not. So, you need to make sure that your lungs are in good working condition, your kidneys are in good working condition, your liver is in good working condition, your heart is in good working condition. So, whether you're able to get up do stuff, whether you get short of breath with minimal exertion. Again, with this disease it's a little harder to identify that without doing specific tests because you might be short of breath because of low hemoglobin and the other thing that we have to do in addition to making sure that the organ function is adequate is to make sure that there's a donor available and to do that we take a blood sample from you and if you have brothers or sisters who we determine are healthy enough to be donors for you it's a simple blood test that we do for them or like even a cheek swab that gives us an idea whether they match you. We look at about places where we look for the match and each brother or sister since you inherit one set of chromosomes from your mother and one from your father, there's one in four chances that any of your brother or sister could be a match for you and obviously if you have a bigger family more brothers and sisters the higher likelihood of finding a match in the family, but for people who since this is a disease of in the sixth and seventh decade, your siblings are probably in that age group they might have other medical conditions. So, we then also based on your actual typing, the eight spots that we look at we can run your actual type against the 16 million people that agreed to be donors for people who either don't have siblings or whose brothers and sisters are not a match to see if there's a donor identified in the registry and if we do have a donor identified in the registry and your organ functions are in good condition and clinically it's indicated to proceed to a stem cell transplant then we would go ahead and contact the donor, the master marrow donor program we contact the donor. They will have an information session at a transplant center where the physician will explain to them what it means to donate stem cells because it's no long lasting effect that they have with the stem cells (inaudible 1:36:40). It's not like giving away your kidney or something, but it is a process that they have to go through of whether we collecting stem cells from the marrow or are we getting it from the (inaudible 1:36:49) blood. So, they have an information session. They have blood work to make sure that they are healthy enough to donate and they don't have any diseases that they could transmit and once that's determined and you're in good condition to go through the transplant, you'll be

admitted to the hospital. You usually get chemotherapy and/or radiation for the first few days when you're in the hospital. After that you get an infusion of stem cells and it's like a blood transfusion. It's not a surgery that you go through and once you have that transfusion of the stem cells, you can think of those stem cells as having these little hooks on them and they circulate in the blood. They know when they get to the marrow that that's home. They hang around there and start making normal blood cells and that period of time it usually takes us about 10 days to 2 weeks while your counts are very low and we have to support you with blood and platelet transfusions, antibiotics to prevent infections. There's a high likelihood of getting infections during that time. So, we might have broader spectrum antibiotics during that time to prevent infections or treat infections and usually around day 10 to 14 is when we start seeing the blood counts coming up and after that we start switching medications that you're on to from IV to oral forms and even though we find a perfect match for you these are still somebody else's cells in your body. So, what we worry about with the stem cell transplant is what we call graft versus host disease as in the cells from the donor trying to attack your normal tissues. So, your normal skin, your blood, your liver and to try to prevent that we have the autoimmune suppressive medications which usually you're on for about 6 months after transplant and then if there's no graft versus host disease or there's minimal graft versus host disease we can start tapering off those medications. A little bit graft versus host disease is a good thing because it keeps the abnormal cells from coming back because the (inaudible 1:38:36) care initially but there's still some cells left over in your body and they might try to grow again, but a little bit of graft versus host disease of donor cells keep those cells from growing back but too much of it can be fatal if you people get very aggressive graft versus host disease it can be to the point that it can be fatal. So, that's the reason why we have to kind of make sure that we have an information session with the patient that they understand what the risk and benefits of going through that procedure is. So, that's kind of a 5 minute talk for what transplant is usually we sit down with patients for the few hours to go over everything that should be expected with the chemotherapy with what to expect. We usually give out a binder to the patient so they can go home and read and usually patients will need a lot of care post transplant. So after they go home with the transplant they come to the clinic 2 or 3 times a week initially because they are on so many medications we need to watch for so many things. Medications need to be adjusted. They need to have somebody who can take care of them. They can't be living by themselves because somebody will have them drive to the appointments, make sure they're taking the medications appropriately. If they get any infections bring them to the hospital. So, those are other things that we have to make sure the family understands to what the commitment is in terms of going through the transplant.

Q8: Thank you.

Q9: What about the procedure that's not as intense?

Dr. Deol: So, we have what we are trying to do with the transplant with the newer things that we've worked on transplant is to reduce the intensity of transplant in terms of the main concern for the... so, there's even if brother or sister is a full match for you and you're in perfect condition going to the transplant there's about a 15 to 20 percent chance of somebody not making it through in the first 3 months of the transplant because of some of the complications that we briefly mentioned. So, what parts that if we reduce the amount of chemotherapy that we give you before the transplant maybe we can reduce the (inaudible 1:40:38) of risk. So if you go

back when we started doing transplants, the first few months mortality was as high as 30 – 40 percent. We've cut it down significantly over the last few years with help with supportive care and also tailoring the preparatory regimen that chemotherapy and/or radiation that's given before the transplant down. So, what we call the reduced intensity initial regimens that are more appropriate for patients in the age group that Myelodysplastic Syndrome is usually identified and we try to do also do things that we were just talking about like Azacitidine or other agents post transplant because what our thoughts are if you don't do the high dose chemotherapy up front maybe you slightly increase the risk of relapse later on because the cells might be left over. So, what we're trying to do is to try to do things after transplant to try to make sure that those cells stay suppressed and the donor's immune system donor cells have enough time to make sure that they take care of all the cells that might be left over. There's a lot of things that we're doing in terms of reducing the intensity or the rigors that people have to go through with the transplant with the chemotherapy initially and that's what causes most of the complications with the transplant.

Q9: Thank you.

Q10: Does an abnormality on a specific chromosome dictate prognosis on your survival more than another? For example, I have 2 abnormalities of chromosome 15.

Dr. Deol: So unfortunately, we don't have information about every and each chromosome of abnormality there may be. If you have more than 3 chromosome abnormalities we know that's it was that increases the risk in terms of when we grade the based on your chromosome changes. There are certain chromosomal abnormalities that even having 1 like -7, -5, those are chromosome abnormalities, models (inaudible 1:42:28) we call them (inaudible 1:42:29) karyotypes. Those are much higher risk compared to some of the abnormalities that people might have. So, it's based on you have... You said you had 15 and what was the other one?

Q10: Two chromosome abnormalities on 15. Translocation as well as monosomy.

Dr. Deol: And how many cells did they say?

Q10: I don't know. I don't know what you mean by cells.

Dr. Deol: So usually like we were just talking about they look at about 20 cells. If all 20 cells have the abnormality that means that something that's inherent to the makeup...

Q10: Cellularity?

Dr. Deol: No. It'll probably be in the cytogenetic report. It usually will say 20 out of 20 cells have this abnormality or 5 out of 20 cells. Sometimes 1 or 2 cells might have that abnormality and it does prognosticate, but if all 20 cells have that means more than if 1 or 2 cells have the abnormality and, again, like I said, it probably will be beneficial to see what the progression of the disease in terms of how things are going because with these individual like with the 15 chromosome abnormalities there's not a whole lot of data that we have in terms of how those patients and usually will do. Questions?

Q11: Do continuous phlebotomies, putting these... the word strain on your bone marrow to keep bringing back (inaudible 1:43:57).

Dr. Deol: Usually not. Again like in your situation like you said, you had hemochromatosis. So, you're getting (inaudible 1:44:04) to keep the iron levels low. That doesn't put like... what is going to happen with your red cells eventually is going to be more dictated on what they are chromosomatically or genetically destined to do rather than how many times they have to divide.

Q11: If you have too many, though, and your ferritin level keeps going down, can you lead yourself into leukemia or...?

Dr. Deol: The body would be like if nobody's monitoring your iron levels and stuff with continuous phlebotomy, it could get to the point that you become iron deficient even though you might (inaudible 1:44:42) you can become iron deficient, but that's the rarity than the rule. And I'll be around if (inaudible 1:45:00) have to go upstairs and see some patients, but I'll be around later on if you have more questions and stop by later in the day.

?: Thank you.

(Applause)

(General chat 1:45:12 - 1:48:07)

Emily Knight: So, we can get going. My name is Emily. I'm a nurse in hematology oncology at Mayo Clinic in Scottsdale, Arizona. Came here with the MDS Foundation to present to you guys *The Building Blocks of Hope* which is a binder that everyone should have gotten. I think we had enough for everyone. In the inside of the binder, there is a questionnaire that we just ask that you fill out, take your time and we'll collect it at the end of the forum today. What *The Building Blocks of Hope* does is it's a guide for patients and caregivers to basically living with MDS. It's a global print and online patient advocacy initiative that provides a personalized, educational program for patients and caregivers to prepare, participate and live with MDS. The colors of *The Building Blocks of Hope* include Tucson teal, Navajo red and desert sand. They're reminiscent of the southwest landscape with beauty of the night sky over the sand swept deserts and stunning mountain ranges. The colors represent warmth, stability, healing, passion and protection. The colors form the base for *The Building Blocks of Hope* logo constructed in a wave-like pattern indicating the fluidity of life, health and illness. The single red band which continues up the plant symbolizes strength and improvement of bone marrow function. The idea of hope for the future and extension of life is emulated in the sprouting plant. What is put together by the MDS Foundation and the group, the Nurse Leadership Board. So, there's people from the United States and all over the world who help put it together. The goal is to answer common questions you or your family members may have about MDS to help you understand the diagnosis and how it's diagnosed, what your treatment options are, common side effects of treatment and what can be done to control those side effects, what new treatments are on the horizon, consequences of blood transfusions and should you receive iron chelation therapy, how do you select a bone marrow transplant center if that's an option for you and how can you keep yourself healthy.

So, some tools and strategies for success. We'll explore *The Building Blocks of Hope* and that will hopefully help you understand your disease, know your IPSS and IPSSR risk category and help you ask questions about treatment like what the treatment schedule would be, what are possible side effects, how are you going to manage those side effects and then you have to consider, you know, any lifestyle changes that may come into effect, transportation issues going to and from appointments. Know that you can ask for help. Stay connected with your doctor, the MDS Foundation, there's support groups out there for you. Become a partner in your MDS journey and build your MDS plan. The binder, *The Building Blocks of Hope* will hopefully help you to track your progress, track your disease.

So a lot of this will be a little bit of review from Dr. Deol's presentation, but we'll go through it and it is in your binder as well.

What is MDS? So, the Myelodysplastic Syndrome represent a group of myeloid lineage bone marrow disorders, bone marrow cancers. It's not one disease, but a group with variations in clinical findings, disease trajectory and treatment recommendations. So, every patient is a little bit different with MDS.

So, what happens? The cells are abnormal in size and shape or dysplastic. These dysplastic cells don't work well which leads to ineffective hematopoiesis which results in cytopenias or low blood counts and like you said, it can be in one or all three of the cell lines - the red cell, white cell or platelets and there is a risk of developing leukemia in some cases. In general, if the disease progresses, the bone marrow function declines. So, this is a picture of a normal healthy bone marrow and so you can see the hematopoietic stem cell. As it matures and divides it either it divides into the myeloid line or the lymphoid line. In the lymphoid line is the lymphocytes, T cells. T lymphocytes, B lymphocytes and the natural killer cells and then the myeloid matures and develops into our white cells, red cells and platelets. This is a picture of MDS bone marrow. So, the stem cell divides into the myeloid and lymphoid line, but the myeloid line does not mature and divide like the normal bone marrow. It produces the immature precursor cells or what you might hear called as blasts and that leads to the cytopenias because the bone marrow is full of these immature cells. The healthy cells can't mature and divide.

So, how is MDS diagnosed? Well, diagnosis is made through a bone marrow biopsy which we talked about earlier, but there are additional tests that your doctor might do to rule out another cause of the cytopenias. So, they'll do the iron studies, B12, folate, erythropoietin level, thyroid, (inaudible 1:54:17) and liver and if all those come back normal and aren't the cause of the cytopenias then they'll proceed with the bone marrow biopsy. They'll check for blasts. They'll check the cytogenetics, iron stains, reticulum stains and then once the diagnosis is established, they'll determine the subtype using the French/American/British or the World Health Organization and then also they'll estimate the IPSS score.

So, this is the classification system. Again, the FAB and the WHO. The International Prognostic Scoring System, the IPSS or IPSSR now, is a system for estimating expected survival without treatment and risk of developing leukemia. Disease related factors associated with the risk and prognosis. It looks at blast percentage, cytogenetics and cytopenias and then your physician will

use this to decide when and what treatment might be best for you. So the IPSSR cytogenetic risk groups. So very good would be a deletion 11Q or -Y and then it gives the estimated survival and, again, that's without treatment. So then there's good cytogenetic risk groups. Normal deletion 20Q, deletion 5Q, deletion 12P and then you have the intermediate. You can see those there. Poor and very poor is complex or greater than 3 abnormalities. So, the IPSSR risk categories that takes into account the cytogenetics, the blasts, hemoglobin platelet and ANC or your neutrophil count and you add all those up and then it gives you a risk score of very low, good, intermediate, poor or very high and then based on your score, it gives you the median overall survival and risk of transformation to acute leukemia and that, again, is without treatment.

So, a few quick facts about MDS. The average age is about 73. It remains incurable. The only potential cure is allogeneic stem cell transplant. The leading cause of death is the disease itself. Risk stratified treatment strategies are key to optimal therapeutic outcomes.

So with MDS, every patient is different. So, it's important to individualize your treatment plan. Treatment triggers would be transfusion dependence if you're requiring platelets on a regular basis, half red blood cells, if your blood counts are progressively dropping, if you have an increased number of blasts or you have high risk disease. Any of those would be an indicator that your doctor might want you to start treatment. So when you're... It's time to begin treatment, they look at your performance status, any comorbidities, the IPSS or IPSSR risk category and then if it's primary MDS or denoble MDS versus secondary MDS from another cancer or radiation exposure. The cytogenetic status and your lifestyle all play a role in picking which treatment would be best for you.

Current treatment options. Supportive care alone. So, transfusions, blood platelets and then growth factors. The erythropoietin Procrit, Aranesp. Revlimid or Lenalidomide if you have that deletion 5Q chromosome abnormality. Then there's the Vidaza or Dacogen. Bone marrow transplant is that... you know, if you're eligible and have the donor and all of that and then there are investigational agents, but as you can see the approved agents are limited. So, it's important to maximize each agent to its full benefit.

This is just a list of some of the investigational agents. Like we've said already, allogeneic stem cell transplant is the only potential cure, though it's not an option for a lot of patients with MDS as it's you're generally diagnosed in 60s, 70s. Also the availability of a suitable donor can play a role into that, but age alone shouldn't exclude active therapies. You have to look at a person's performance status and their comorbidities. Also important to know that all therapies for MDS require time to work. So 4 to 6 cycles, 4 to 6 months. So when you're starting any new treatment, don't expect that first month to see the changes in the blood counts and be feeling better. It does take time and the blood counts often do get worse before they get better. So, don't get discouraged by that.

Proactive management of the side effects in the early phase of the treatment are key to obtaining the best response. Your doctor, your nurse will help support you through those first few months when the blood counts are their lowest.

You can look at why time is required. So before treatment begins, your bone marrow is crowded with the immature cells. It can't produce the regular healthy cells. So, your blood counts are dropping and then when treatment begins, the treatment cleans out the bone marrow. So, it cleans out those immature cells so the blood counts drop further. As you begin to respond to the treatment, your bone marrow will start to recover and it will allow the production of the healthy cells.

Q12: What is the treatment in this case that we're...?

Emily Knight: You can... Vidaza or Decitabine. And so then as the response continues, your blood counts improve. They normalize and you can be weaned from the supportive care, the transfusions, if you're on antibiotics to prevent infection. All of that can be slowly weaned off. Just important to know that those first month 1 to month like 4 or 5 are when the blood counts are going to be lowest and you just got to push through because the treatment still could work.

We said before a minimum of 4 to 6 months. The cytopenias often get worse before they get better, but there are strategies for getting through those first cycles. You have to... Your doctor may delay treatment a little while to give you time to recover. He may reduce your dose of treatment. Supportive care with blood transfusions, antibiotics, just I think having that expectation that things might get worse before they get better is important.

So, this is patients' response after 4 cycles of Azacitidine or Vidaza. You can see that pink is the hemoglobin. After 4 cycles is when it really see the improvement and then same with the white count in blue and the platelet count in the orange. And this is a patient's response over 10 years on Lenalidomide. So, one thing to think about with the Lenalidomide and some of the other treatments even is while your blood counts may be improved and you don't need transfusions they may not be normal. So, it's a new normal for you. This person's hemoglobin is as low as 10 to 11 and then their new normal might be around 11. So, they're not requiring transfusions, but it's not technically normal.

What can you do to stay healthy? This is something that everyone whether you have MDS or not. Eat a balanced diet, exercise, avoid infection, avoid bleeding and then I think important to continue to enjoy the things you know you love. Get enough rest and then take advantage of the available resources. *The Building Blocks of Hope* is a great new resource that we hope you'll find useful. Don't be afraid to ask for help whether it be through your doctor's office, reach out to the MDS Foundation. There are people out there, support groups that want to help you.

So, building your MDS plan and this is in *The Building Blocks of Hope*, the binder you got. Tab 1 is Understanding MDS. It's a complete description of the disease process and hopefully will help answer some of the common questions you may have. Tab 2 is the Seeking Treatment tab. Treatment for MDS can vary based on the type of MDS you have. This section provides detail about various approaches. Tab 3 is the Quick Tips. Quick tips offered in this section include guidelines for monitoring and managing your symptoms. Tab 4 is Iron Overload. Iron overload is a possible outcome of receiving multiple and repeated red blood cell transfusions. This tab will answer common treatments for that and then Tab 5 is the My MDS Plan. Understanding the diagnosis of MDS will give you or your caretaker an active part in your individualized treatment

plan. Provides several tools to allow you to track and manage your journey. There are blank tabs, so it might be helpful before you write on them to make some additional copies. That way you won't run out of copies. Tab 6 is the MDS Foundation. It talks about what the MDS Foundation does and what it can help... be there and do for you and then just would like to acknowledge the contributors to the... who helped contribute to *The Building Blocks of Hope*. Patient and caregiver contributors along with the MDS Foundation and MDS staff. So, we do have time, so any questions that anyone has?

Q13: Just wondering. We're from Windsor, Ontario and at the cancer center there there's hardly no information about MDS and when we first were informed about that we went into the resource center and I don't think we were even sure what the doctor had said, but we didn't find any information and since then I've found huge amount of information, which is wonderful but nothing is in that center in Windsor and I'm just wondering why.

Emily Knight: Well, what you might do is speak with your doctor or nurse or if they have clinical educators there and bring that up to them because they can get the information from the MDS Foundation. They can see what's available, order it.

Q13: We will do that.

Emily Knight: So they can have that to give to patients because having the information is important in (inaudible 2:06:43). Anyone else have questions about the binder, about MDS, anything?

Q14: Yes. Early in your discussion you made the statement MDS, the cause of death is the disease itself. Would you elaborate on that?

Emily Knight: Yeah because sometimes people think that the cause of disease... or the cause of death would be transformed into acute leukemia or getting other comorbidities, but in fact it's people with MDS sometimes have it for years and eventually they die of the MDS, the low blood counts. That's what ends up taking their life.

Q14: So as you just said, it's usually the low blood count.

Emily Knight: Right. Right. When you're... When the MDS progresses, the blood counts decline. The white blood cell count... You may get an infection, you may require repeated transfusions, platelets... platelets and blood.

Q15: Is there any homework that (inaudible 2:07:59) since they come out with this?

Emily Knight: Not that I'm aware of. I don't know. I just know the approved FDA treatments. I can't say if there's alternative therapies. None that I'm aware of.

Q15: Because my husband's doctor suggested turmeric is like a spice.

Emily Knight: I heard of that, but I don't know exactly the mechanism on how it works and if there's been any studies to prove its effectiveness. I don't know if anyone else has heard anything.

Q15: I've heard of it as a... to prevent things. Not sure once you've already... how much it can help you once you've already (inaudible 2:08:47).

Q16: Currently there's trial going on at UMass Medical exactly on that for those with low risk MDS and I'm trying to get into, but our doctor hasn't yet made contact.

Q15: Oh. Where at?

Q16: UMass Medical. It's in... near Boston. The thought is that these high, high doses... dosages of a nontoxic thing like turmeric can prevent the progression of the disease. It's a combination of turmeric and Gingerall.

Q17: The cumin too he was saying.

Q16: Cumin is related to turmeric.

Q17: Right. It's a... Well, I'm getting the combination in the (inaudible 2:09:34) right now and also you can get the spice and put it in your food. So, we've been doing that, but don't know if it really helps or not.

Q16: Early on in the clinical trial, they're saying that they've seen pretty good results.

Emily Knight: She was saying for low risk MDS, there's a trial using turmeric and Gingerall and that's at University...

Q16: UMass Medical.

Emily Knight: UMass Medical.

Q18: What was it?

Emily Knight: Turmeric.

Q18: And general?

Q16: Gingerall. I guess it's probably ginger.

Emily Knight: And so the thought is it would slow the progression?

Q16: Yes and it's specifically targeted for those with low risk MDS. Those that have progressed beyond this isn't going to work as a preventative for further progression. It's just for those with low risk.

?: (inaudible 2:10:31) with your immune system.

Q?: Which is shot to begin with.

Q16: I have the article with me from UMass if anybody wants to read it while you're here.

Q?: Yeah. I would.

Q17: Is there a copy machine around here?

Emily Knight: Yeah. I'm sure we can find one to make some copies. Anyone else have any questions, comments? We can take the... Lunch will be here at noon. So if you want, you can take the few minutes here and fill out the questionnaire that's in the binder if you've done that, just get up and wander around.

(General chat 2:11:13 – 4:05:01)