Speakers:
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Emily Knight, RN: I think if everyone's ready, we'll go ahead and get started. My name's Emily. I'm a nurse from Mayo Clinic in Scottsdale and I'm on the MDS Nurse Leadership Board. So, we're excited to be here today to talk to you guys about MDS. First up, Dr. Liesveld will give her presentation on MDS and then we'll have some open discussion and there'll be plenty of time for questions and then I'll be giving a slide presentation on the *Building Blocks of Hope* and talk about quality of life and living with MDS. So, I'll turn it over to Dr. Liesveld. I think everyone saw the bathrooms are just out the door to the right by the elevators. So if you need to get up at any point…

Jane Liesveld, MD: I feel very far away from all of you, so if you can't hear me please let me know and we're a small group, so I hope this will be relatively informal. So even in the middle of slides if you have a question, raise your hand because I don't have… This is not necessarily a formal presentation, so we're happy to interrupt and answer questions as you go along or otherwise feel free to write them down and ask them at the end. Before I begin, I wanted to introduce you all to Dr. John Bennett who's sitting in the row behind there. Dr. Bennett was one of the original organizers and founders of the MDS Foundation and he is an internationally known expert in MDS particularly as relates to its… the understanding some of the morphologic aspects of the cells that pathologist and hematologists looked at under the microscope and he's been very involved in the classifications and prognostic scoring of MDS which have continued to evolve through the years. So, we're happy he was able to come briefly this morning and what I wanted to do here is try to just give you a little bit of an overview of MDS and I think all of you are probably starting at different… not only different levels of the disease, but also perhaps different levels of knowledge about the disease. So, I want to keep this fairly basic, but if you do have questions as I go along about some of the terminology or some of the classifications, please do ask about that because I do want to make the point that while we use the term MDS as a kind of unifying diagnosis, this really is a very heterogeneous disease as you'll see as we discuss this in more detail. There are patients who have very… what we would call very mild forms of MDS and others who have disease that requires fairly urgent and immediate treatment and a whole spectrum of things in between and throughout this talk we will talk about some of the prognostic indicators in this disease and I think that's one of the valuable things that the MDS Foundation has made available to patients is an ability to look some of these scales from online so that you can kind of see where you might fit or your loved one might fit into this spectrum. I do want to make the point, however, that these prognostic indicators are not perfect measures of where a disease falls in this spectrum and also how the disease will progress on the spectrum. So, just keep in mind as we go along that this a heterogenous disease. Each case of MDS is individual and when you work with your own hematologist or oncologist, you will obviously have a lot of discussion about what is going to be best for you and I think we'll get into that a lot more as we do the discussion part of this morning.

So, many patients with Myelodysplastic Syndrome are first brought to a physician's attention because not only based on symptoms but also abnormalities that might appear on blood counts that are checked either routinely or in response to symptoms that a patient would report to their physician and I put this slide up just because most patients with MDS particularly those who have what are called low grade forms will present to their hematologist with a whole host of symptoms and blood count abnormalities and it will be the job of the hematologist to sort through a whole list of diseases that are possibilities to explain those abnormalities and that's why many patients, I think, aren't immediately diagnosed with MDS even though they may present with, for example, of low red blood cell counts or low platelet count. There can often be some delay in the diagnosis as the physician sort through what's called a differential diagnosis meaning bringing to mind all of the possibilities in terms of diagnoses that could explain what the patient is presenting with. So, there's certainly deficiencies of vitamins and minerals like iron that can explain anemia. Some patients due to alcohol consumption or other medications may have lowering of their blood counts. A condition called megaloblastic anemia can sometimes be mistaken for MDS or vice versa and there are a lot of other chronic medical conditions such as kidney problems, various inflammatory states and other cancers and leukemias that can also cause some of these same changes in the blood count picture. So, when a patient presents to a physician before the diagnosis of MDS is made and before that diagnosis is pursued, there are a lot of other diagnoses that are entertained by the hematologist and as many of you are aware in order to pursue the diagnosis of MDS other tests that just more examination of the blood smear and of the bone marrow is required to make that diagnosis. Many patients do present with anemia and I think this slide is just interesting because as many of you are aware, Myelodysplastic Syndrome does tend to be a disease that occurs as patients age and I think this graph which comes from an article in *Blood* from a number of years ago, just is interesting because it shows that while in the younger populations, it's females who have the highest incidents of anemia and that's due to menstruation and pregnancy. As the population ages, it's actually males who have a higher incidence of anemia and that's also reflected in the fact that more males than females aren't diagnosed with Myelodysplastic Syndrome particularly through the aging spectrum. So, anemia is a very common presentation for Myelodysplastic Syndrome, but other patients will present with abnormalities of other blood counts.

So, that leads us to the question what is Myelodysplastic Syndrome and I think of all the diseases that we see in hematology oncology. This is sometimes one of the most difficult for patients to understand and also for us as physicians to be able to convey to patients and their family members because while this often can present in a relatively indolent chronic fashion with simple abnormalities of blood counts, Myelodysplastic Syndrome really is what we call a clonal disorder meaning it is an abnormality of a stem cell in the bone marrow that has potential malignant features and that hence the word clonality meaning that all of these cells arise from an abnormal original stem cell and often when we look at the bone marrow in Myelodysplastic Syndrome it will still have a lot of cells in the marrow even though in the blood there will be lowering of the blood counts and abnormalities of the function of those cells that are circulating

in the blood. So many patients with Myelodysplastic Syndrome will present with low blood counts even though in the bone marrow there is a lot of cellularity and the marrow is trying to produce the normal cells that are needed for infection prevention, prevention of anemia and prevention of bleeding. So, the dominant feature in Myelodysplastic Syndrome is that there is essentially a bone marrow failure state because even though cells in the marrow aren't proliferating and growing, these cells aren't effective. They're not being released into the blood stream to function normally and there will be lowering of the blood counts and in addition to the lowering of the blood counts because this is a clonal disorder or an abnormality of a progenitor or stem cell in the bone marrow, these stem cells do have a predilection to evolve into an acute leukemia and as we'll talk about later that predilection is different based on the type of MDS that a patient is diagnosed with and up till very recently in the last decade when three different drugs were approved by the FDA for the treatment of Myelodysplastic Syndrome, supportive care meaning transfusion support and observation and other means to support blood counts has really been the standard of treatment as we've gone along.

MDS is as hematologic diseases go, really one of the more common ones it's estimated that there are about 20,- to 30,000 new cases per year in the United States. This is just in the adult population. Rarely we see Myelodysplastic Syndrome in a pediatric population and even though the disease acute myelogenous leukemia gets a lot more press and probably more funding support and publicity, Myelodysplastic Syndrome actually outnumbers the number of new cases per year that are diagnosed with acute myelogenous leukemia in this country. As we mentioned before, it does tend to happen as patients age. The medium age at onset is greater than 60. In some studies, it's been actually in the 70s more recently and as we talked about the incidence is greater in males than in females. No one is certain why that's the case. In the past it was thought perhaps that was due to occupational exposures, but as females now are entering the workforce in many of these previously male dominated professions, it will be interesting to see with time if epidemiologically more females will now be diagnosed with Myelodysplastic Syndrome and the incidence does continue to increase with age and as we've talked about this as a whole spectrum of diseases, so some patients who are diagnosed in advanced stages have a short survival time whereas other patients can live many years with this diagnosis and this just indicates, again, that MDS is a disease of aging. As you can see, there are patients who are diagnosed at younger ages, but the peak incidents is in the 70s and 80s and in terms of incidents per number in the population. So, this is a disease that of the older population and as the older population increases in size in this country and worldwide, it's expected that that incidence of Myelodysplastic Syndrome will also increase.

Now many patients when they're first diagnosed with Myelodysplastic Syndrome will ask what caused this. Unfortunately, in the current era, we usually are not able to come up with an ideology or a specific cause. As we mentioned, the greatest risk does appear to be advancing age. Some of the patients who are diagnosed with Myelodysplastic Syndrome will have had previous treatment for other malignancies and this is a state that's called a secondary Myelodysplastic Syndrome and any sort of previous chemotherapy especially medications like nitrogen mustard

which was used in the past for acute (inaudible 12:57) disease, other chemotherapy drugs as well as radiation can predispose eventually to the development of Myelodysplastic Syndrome. There have been some studies that have suggested a relationship to exposure to certain environmental toxins such as benzene or other organic solvents, but many times in many epidemiologic studies these associations haven't been that strong. Perhaps except for benzene and its association with acute myelogenous leukemia but in, obviously, most patients there are not these types of exposures and even if there are it's often difficult to show a direct relationship to the incidence of Myelodysplastic Syndrome. Cigarette smoking has epidemiologically been shown to be associated with Myelodysplastic Syndrome and there are other congenital and familial disorders which could show up as MDS in a younger population, but that's really quite rare.

Now, how do patients with MDS present? As I mentioned before, many patients will come to their physicians with really no symptoms, but may have a routine laboratory test as part of their yearly physical exam and maybe found at that point to have abnormalities of the blood counts that would eventually lead to this diagnosis, but apart from those asymptomatic patients, many patients with MDS do present with fatigue. That's really probably the most common symptom and I think we'll be talking more about that as we get into our discussion later, but because of the abnormalities of other peripheral blood counts that occur in myelodysplasia, patients can present with easy bruising related to either low platelet count or abnormal function of platelets. Nosebleeds and gum bleeds can be a common manifestation. A few patients will present with a rash. Sometimes this is, again, related to low platelets, but others have other sources of skin abnormalities. Related to the anemia, some patients will be short of breath or have a rapid heart rate. Some people will report weight loss or low grade fevers or loss of appetite and some patients will have had frequent infections if they have some abnormalities of their white blood cell counts. So while all of these form a constellation of symptoms, none of these symptoms by themselves are sufficient to point to MDS, but obviously, MDS does enter into the array of diagnoses that a physician would be considering if a patient presented with these symptoms in the context of some abnormal blood counts, but as we talked about earlier there are a lot of other causes of anemia. Other medications that can suppress blood counts and other viruses such as hepatitis or the AIDS virus, Human Immunodeficiency Virus or other chronic viral illnesses that can sometimes masquerade much like MDS.

So in making the diagnosis of MDS, not only will your physician look at your blood counts and at your blood smear, but to make the diagnosis it really does require obtaining a bone marrow aspirate and preferably also a bone marrow biopsy and the bone marrow needs to show evidence of abnormality in all of these cell lines or at least in one of them in order to make a diagnosis of the Myelodysplastic Syndrome and often as we mentioned the marrow is going to have a lot of cells and the pathologist who reviews the slides of the bone marrow is going to be able to tell if these cells have features of dysplasia and typically that will be seen in more than one of the blood cell types and I actually have some slides from actually from Dr. Bennett showing that in each of the cell types there will be abnormalities and I'm not going to go into these for you, but just to give you an idea of what your pathologist will be seeing under the microscope, they will

be looking at the cells that eventually form the red blood cells. You can see these pale red blood cells in the background here and all these other bluish cells or purplish cells that have these nuclei are the cells that eventually will form those circulating red blood cells and what the pathologist will be looking at in the marrow are features of these progenitors of these red blood cells to see if there are any abnormalities there. So, they'll be looking at features of the nuclei which are these large purple areas in the cells as well as features of the cytoplasm and whether there are any forms of inclusions or other abnormalities in the cytoplasm. Based on these appearances, they will be able to issue a diagnosis of Myelodysplastic Syndrome and not only will they be looking at the red blood cells, but they'll also be looking at all of the white blood cells in the blood smear and in the bone marrow and this is their slide of the white blood cells in the marrow and what they'll be looking at are these cells that shown here by the arrow which are called neutrophils. These are the cells that will eventually be released into the blood and will help to fight infections and often in Myelodysplastic Syndrome, the neutrophils don't develop a normal nucleus and their cytoplasm doesn't have as many granules which are of aid in fighting infections as would a normal cell. So, these are just some of the features that the pathologist will be looking at in the bone marrow. They will also be looking to see if there's an increase in a cell that looks like this. This is what's called a blast cell. This is a cell that would normally develop into one on the three blood lineages of red cell, white cell or platelet that this is probably a blast that would be going down the white blood cell line and as you can see it's got a really big nucleus that takes up most of the cell and the pathologist will be able to see features of this that will allow it to be classified as a blast cell and they will issue in their report a percentage of all these cells that have this feature of looking like a blast cell and that as we'll talk about later becomes important in defining which type of Myelodysplastic Syndrome is present. So, they will also be looking at the cells in the bone marrow that are called megacaryocyte that form the platelets because many patients with Myelodysplastic Syndrome will have a low platelet count when they're diagnosed and, again, I won't go into the details of this, but they'll be looking for specific features of these very big cells in the bone marrow that are going to spew out little platelets that go into the blood stream and looking at how those may look abnormal or dysplastic.

So as MDS was originally defined and as the understanding of it has evolved through the years, there have been many different classifications and prognostic systems that have been generated to try to help us better understand how individual patients should be treated and managed and also to predict what type of course they may have as they go through their journey with the Myelodysplastic Syndrome. One of the classifications that Dr. Bennett was actually involved with and originally describing was the called the French American British Classification because it involved investigators representing all those countries and they put together what was really one of the first attempts to subdivide this disease. The World Health Organization had subsequently come up with a series of classifications that continue to be evolving and, again, to help to better understand these sub-classifications and there also have been many prognostic scoring systems and many of you will hear your physician when you're first diagnosed discuss your IPSS score and we'll go into that a little bit as we go through this.

So the original French American British Classification that was described, I think is still very pertinent because the WHO uses a lot of the same terminology and there have been some subtle changes, but many of you who have been diagnosed with MDS or who have relevance with MDS will be familiar with these terms and what this does is has it subdivides the disease into those that involve primarily anemias, the term refractory anemia and refractory anemia with ring sideroblasts which refers to a change in the red blood cells in the bone marrow that the pathologist is able to see during the bone marrow examination and then based on the percentage of the blasts that are in the marrow, there's the classification called refractory anemia with excess blasts. In that classification, those patients who had blast counts that were near the level at which we would make a diagnosis of leukemia were called refractory anemia with excess blasts and transformation and this classification also included chronic meylomonocytic leukemia which in many instances has behavior like a Myelodysplastic Syndrome.

So, that was one of the original classifications of Myelodysplastic Syndrome. It's still in use today as it relates to the World Health Organization and I won't go into the details of this slide, but I think it just shows that the survival based on these individual classifications was very predictive and gave validation to that classification. The World Health Organization subsequently took that classification and refined it somewhat. They put in classifications that encompassed other abnormalities in other cell lines such as the white cells and platelets and they also redefined that classification called refractory anemia with excess blasts and transformation and put that into the classification of AML as being marrow that shows more than 20 percent blasts and for chronic meylomonocytic leukemia, this is still included in the MDS umbrella, but it was also recognized that some patients with that disorder have elevated white count that puts them into a disease category that's actually called the myeloproliferative disorders instead of the myelodysplastic disorders. So, this is a classification system that's also in use today, but is one that continues to evolve.

Now in 1997, Dr. Greenberg and colleagues put forward what was called the International Prognostic Scoring System and at that time that was really the most comprehensive scoring system for MDS that was available that helped patients and physicians to be able to prognosticate for an individual what their course with their disease might be and this stratified patients into 4 risk groups that were based on estimated survival times and as well as the risk of that patient to have transformation of the disease to a full blown leukemia and this scoring system was based just on the percentage of bone marrow blasts, the patient's chromosome abnormalities that were present and also the number of cell lines that were low looking at the white cells, the red cells and the platelets individually and we won't go into the details of this because I want to spend a little bit more time on the revised prognostic system score, but this just points out that this original scoring took into account the percentage of marrow blasts, the type of chromosome abnormalities that were seen when the bone marrow cells were evaluated by the pathologist to see if there were any structural abnormalities in the DNA or chromosomes of that marrow and also the number of cell lines that were low in an individual patient and then it took all of these scores and put them into a prognostic categorization and as you can see that

categorization was able to predict a median number of years that patients would live with the diagnosis and, again, I want to emphasize these are just medians meaning that there are patients with low MDS and scores who can live for 20 years or more. There are patients with high risk disease who also live longer than this, but this happened to be the median survivals which are shown over here and also this was very predictive of the risk of an individual patient or an individual class of patients transforming to AML with number of years to that transformation shown in this category.

Again, I won't dwell on this, but this was just the classification of the chromosomes that were utilized in this original prognostic scoring system and many of you have been diagnosed with MDS or have family members who have been have probably gone of this information with your physicians, but there are good intermediate and poor chromosomal abnormality categories and as you can see none of these is that prominent. Most of them occur in only 5 to 10 percent of cases and some patients with Myelodysplastic Syndrome will have normal chromosomes or other abnormalities that are much less common but also have to be somehow pigeonholed into these categorization types and this, again, just points out that this original prognostic system was really very predictive in terms of predicting not only the risk of transforming to acute leukemia, but also in predicting overall survival with the disease, again, on a population basis. Since that original prognostic system was published in the late 1990s, there have been many attempts to improve upon it. The World Health Organization also came up with its own prognostic scoring system, the MD Anderson Cancer Center had a prognostic scoring system and there was another one that was published that took into account how many transfusions an individual patient had had, but recently there has been a revised IPSS system published and this is probably the one that to date has the most predictive power for predicting overall survival as well as survival free of transformation to leukemia and for those of you who are interested this was published in the journal *Blood* and in addition to this revised classification there's also an age adjusted score that can be computed. For those of you who are facile with the MDS Foundation website, it allows you actually to put in your own data and calculate your own score and in order to that you'll need to know which cytogenetic classification that you would fall into and as you can see from this list here, this has been much more refined and expanded compared to what was utilized in the original IPSS classification scores and we won't go into these details, but there's a lot more detail provided in this scoring system and then in addition to the chromosomes, again, the percentage of blasts that are in the marrow not only this time lowering of counts paid attention to, but that's more precisely defined, again, to give some refinement of these types of scores and then based on a calculation, again, there will be risk categories that can be computed and these, again, are also predictive of the survival of patients in terms of low to high risk categories and also predictive of the possibility of transformation to acute myelogenous leukemia and we won't go into more of the details of that right now, but these are things that each individual will go over with their own physician in terms of where in this prognostic schema they would fall.

And that brings us to the fact that in MDS, most of the causes of death have to do either with complications from low blood counts and others have to do with the transformation of the

disease to acute myelogenous leukemia and there are also many patients with low grade MDS who will live long enough that they'll die of something else. It could be a heart attack, some other chronic or acute illness. So, not everyone with MDS dies specifically from MDS, but of those who do the main risks are either leukemia or dying from complications related to low blood counts.

And that brings us then to how do we manage MDS in the hope of dealing with these complications of the low blood counts and observing for the risk of transformation to acute myelogenous leukemia and hopefully having some impact on that. So as you can guess because this is a whole spectrum of diseases, depending on where an individual falls in that spectrum, the goals of treatment are going to be very different. So for patients who have low risk disease based on these prognostic indicators or how they're feeling and how their blood counts look, the goal will just be to maintain the blood counts and to assure that those are adequate. So, the clinical endpoints are going to be to see if we can get improvement in those blood counts and also there the emphasis is really going to be on quality of life and we'll be discussing that a lot more later in the discussion. So the management might include things like transfusions, growth factors to stimulate various cell lines and some patients may go on certain medications and we'll talk about that a little bit later. Whereas for patients who have higher classification MDS in the Intermediate 2 or high level per the IPSS score, the goal here is going to be to focus on doing things that are going to improve survival with the disease because in these classifications, survival would be shortened as compared to the general population. So here, we're going to be looking for treatments that are going to allow an improvement in the dysplasia or what we call a complete response or even an improvement in those chromosome abnormalities that may be present and in this category we'll be looking into things like various medications such as Azacitidine or Decitabine, allogeneic stem cell transplant or sometimes even chemotherapies that are similar to chemotherapies that would be used in treatment of leukemia.

So, this slide just makes a point that in MDS the types of treatment that we have are varied and sundry and range from things like transfusions to support red blood cells and platelets, antibiotics, growth factors to stimulate red cells which is Erythropoietin or Neupogen or granulocyte colony stimulating factor can be used to stimulate white cells. There are now new agents that stimulate platelet production and they're called thrombopoietin receptor agonists and there are now clinical trials going on to see of those will improve platelet counts in Myelodysplastic Syndromes. We'll talk a little bit about the hypomethylating agents which have had impact in this disease. These are the two that are approved right now are Azacitidine and Decitabine. There are other novel agents that are being explored and as we talked about in some of the more advanced classifications of MDS either chemotherapy or stem cell transplant can be utilized and, again, the goals of treatment here are going to be we have to select the best therapy that's going to be suited for the individual who presents to us and we have to take into account a lot of different things: how well the patient is doing overall, what other medical problems do they have, what level of MDS do they have based on those classifications and the prognostic scores that we talked about and quite frankly for many of our… particularly really older patients

who are in their 80s or 90s and they have a lot of other medical illnesses, the frequency of visits really becomes a big factor, too, because some of these people have mobility or transportation issues and if they have to come in every day for a visit during the weekdays, that just isn't feasible. So all of these things have to be considered as we individualize treatment for each of our patients. We obviously want to minimize toxicity. We do want to improve blood counts and improve the quality of life and hopefully for those who have high grade disease, we're going to be able to come up with treatments that are going to be able to prolong survival, delay that chance that the patient will transform to acute leukemia and in certain cases particularly in our younger patients who are going to be able to undergo stem cell transplant there is even the possibility of curing the disease.

So, the treatment algorithms are really going to vary on a lot of factors. Some of the things that we have to ask ourselves when we're first meeting a patient with MDS is is this patient going to eventually be a candidate for stem cell transplant should that ever be required and patient age and prognostic score index are obviously going to be important, too.

And I'm not going to go into this, but I just want you to be aware that when your hematologist or oncologist sees you there are a lot of pathways that one can go down in terms of treatment and some of these are what are recommended in terms of national and international guidelines, but as I mentioned each individual has to be dealt with as an individual and the treatment has to be individualized, but this just gives you an idea of some of the thought process that a physician would go through, for example, in a low grade MDS in terms of deciding is just supportive care with transfusions enough, for example, or do we have to go down the line of using growth factor support such as Erythropoietin or other medications that are approved for MDS? And the same is true in the high risk category. Again, here the decision tree is primarily based on is stem cell transplant going to be a possibly for that individual and if it is then, obviously, looking into that possibility or doing other chemotherapy or other medication interventions, but if that isn't going to be possible then there's another whole line of treatments that can be utilized.

So, we have to keep in mind as we do treatments, there is no treatment for MDS and probably for anything else for that matter that doesn't have potential risks or toxicities. So as we think about even something like anemia which can cause fatigue, cardiac and pulmonary problems and we have to be thinking about what are the consequences of our treatments and so when we do transfusion management not only are we improving blood counts and hopefully taking away some of these symptoms, but we're also potentially causing other problems. Every time we give a unit of blood that has about 250 milligrams of iron and as patients have more and more transfusions, there's risk for iron overload which can damage organs like the heart or the liver or other organs and we have to keep that in mind and possibly introduce ways to chelate or bind the iron. Also, we have no transfusion is really without potential complications and that some patients have problems with the fluid that is involved with administration of the transfusion and there also can be allergic reactions. So, all of these treatments even as simple as a blood transfusion have potential long term risks and complications and we just have to keep that in

mind as we go forward. So even transfusions aren't really a perfect solution to MDS. As I mentioned, there is the risk of the iron overload. Because most of these patients are anemic, we can't just draw off the blood to get rid of the iron. So, we do have to in some cases introduce medications that will bind the iron and many of you are familiar with those through things like Desferal and other oral iron chelating agents that have recently been improved. Also, there is a low risk for transmission of infectious disease with blood transfusions. The blood supply is very well screened, but these risks are still present and then as I talked about there can be allergic transfusion reactions and unfortunately in this country, blood isn't free. Even though we have a volunteer donor supply, there are a lot of costs that go with this and transfusions as some of you who probably gone through transfusion know this has a real impact on, I think, quality of life because each transfusion even though it has the potential to improve symptoms also means that you have to come into your doctor's office or the infusion center and spend several hours to receive these transfusions.

So, when we're dealing with patients who have low risk MDS not only are we offering transfusions, but we can also think about utilizing some of the growth factors like Erythropoietin to improve symptoms and some patients with low risk MDS are also treated with 5-Azacitidine in the hope that this will also help to improve blood counts. Now, the agent that's available to improve red blood cells is Erythropoietin. There are 2 different versions of this, one called Epoietin and the other is Procrit and this will improve anemia in a small percentage of MDS patients and interestingly, however, the greatest benefit occurs in those patients who probably need it the least. So, those patients who really aren't needing a lot of transfusions are the ones that have the best chance of response and for some patients who don't respond to Erythropoietin by itself interestingly addition of Neupogen or granulocyte colony stimulating factor to stimulate the white blood cells may also improve the hematopa in a higher percentage of patients. So, it's important if you and your physician are thinking about starting Erythropoietin to consider not only what the transfusion requirements have been, but also to realize that if your blood Erythropoietin level is greater than 500, your chance of responding to Erythropoietin injections is much less whereas if your level is less than 100, there's a better chance of that and a group from Sweden, Dr. (inaudible 42:45) Lindberg was the leader of this study was able to kind of, again, apply a score to patients and this is based on how many transfusions a patient was needing and also what the Erythropoietin level was and that helps an individual patient and a physician to decide about whether there might be a good chance of responding to Erythropoietin. There are a lot of ways to give Erythropoietin. A lot of dosing. A lot of physicians start with 40,000 units weekly and, again, that will improve quality of life in some patients and there's also a longer acting Erythropoietin called Darbepoetin. The advantage of this is that it doesn't need to be administered as frequently and many people like that because it's not only fewer shots, but fewer trips to the doctor's office to see that.

Now, I just wanted to briefly mention there is a type of MDS that's associated with an abnormality in chromosome 5. It's called 5Q- syndrome and the drug called Lenalidomide whose trade name is Revlimid has been extremely effective in this particular patient population. This

was just a case report of a patient who had had over 100 transfusions of red blood cells and then when this drug became available to him had complete reversal of all the blood count abnormalities and became transfusion independent and they were actually able to start doing what's called therapeutic phlebotomy to draw off blood to get rid of that excess iron that had accumulated from all those blood units and this just shows the improvement in the bone marrow and that patient that happened before and after the treatment and that leads to the question does this particular drug work in patients who don't have this particular chromosome abnormality and there are still a lot of studies going on to address that and as I'll mention later here at the University of Rochester we are involved in a national cooperative group study that's trying to assess whether Lenalidomide or Revlimid in conjunction with Erythropoietin will have effect in patients who don't have this 5Q- abnormality and some early published studies have suggested that a percentage of patients may have some improvement in their so-called (inaudible 45:23) response. That is their anemia, but that's much lower than happens in those patients who do have that particular chromosome abnormality and not too many patients became transfusion independent, but enough probably to the point where it makes it worthwhile to look at this.

So in addition to transfusions and Revlimid that's used in that 5Q- syndrome, as I mentioned there are two other agents that are currently approved for treatment in MDS. One is 5-Azacyitidine, trade name Vidaza, and the other is 5-Aza-2'-deoxycytidine, trade name is Decitabine and these are so called not hypomethylating agents because the way they function is that they inhibit an enzyme that blocks the expression of certain genes on many different chromosomes and so allows re-expression of these silenced genes in the hope that this is going to allow some of those dysplastic cells to develop more normally and to start producing normal blood cells.

And this is just a slide that shows the first large phase 3 study which compared the drug Azacitidine or Vidaza to standard care which was transfusions and possibly growth factor support where needed and that took patients on a random basis, assigned them either to that supportive care or to the 5-Azacitidine and then responses were assessed at the end of that. This just shows how this drug does work. It inhibits this enzyme called DNA methyltransferase which blocks the DNA becoming RNA and then various proteins and it's that mechanism that allows cells to hopefully differentiate and grow better in the marrow so that it can produce normal blood cells. So in that randomized study, which had about over 190 patients, there really weren't a lot of patients that went into a complete remission meaning that the Myelodysplastic Syndrome went away, but some patients had a partial response and many patients improved on that arm in terms of their needs for transfusions as compared to only 5 percent in those who were on the best supportive care arm and the other important finding from that study was that in those patients who were placed on the Vidaza, the time to transformation to acute leukemia or to death from the myelodysplasia was much prolonged as compared to those who were on the observation arm and there have also been published several quality of life studies going along with that study that show the 5-Azacitidine actually did improve quality of life in those patients.

Now, also in addition to the hypomethylating agents in certain patients who are of an appropriate age who don't have a lot of other medical problems and who have a suitable donor, we can consider performing an allogeneic stem cell transplant and, again, this is a treatment that isn't right for everyone, but it is something that if you're of an appropriate age if you have sibling donors it is something to discuss with your hematologist oncologist.

This is some data that is a little old now, but really is very comparable in updates from national registries and this just shows that overall survival and disease free survival with this type of approach meaning that a patient undergoes fairly intensive chemotherapy and then replacement of their bone marrow with marrow from either a sibling or an unrelated donor and the long term survival and probably even cure rate with that type of process is about 40 percent which is, again, far from perfect, but for younger patients who have a disease that otherwise be fatal, this is better than can be achieved with supportive care or with drugs like 5-Azacitidine. So for particularly younger patients, this is certainly worth looking into and this is just another way of showing that overall survival curve with patients who undergo stem cell transplant for Myelodysplastic Syndrome and this is a little more current that is you can see the survival is really having to improve since the 1990s, but are still at a 40 to 50 percent range.

There are a lot of different diseases that stem cell transplant is done for. As you can see, Myelodysplastic Syndrome isn't one of the more common ones, but almost all the transplants that are performed for Myelodysplastic Syndrome do are what are called allogeneic stem cell transplants where patients receive marrow or blood stem cells from another donor. In Europe in the past, there was some attempt to use what's called autologous stem cell transplant meaning that a patient's own stem cells were re-infused, but that was associated, as you can guess, with very high rates of return of the Myelodysplastic Syndrome after that procedure. So, in this country and now internationally that type of process is rarely utilized.

So in addition to what we've talked about, there are some patients who will from time of diagnosis go in clinical trials and I would emphasize that's a very valid thing to do because we have yet so much to learn and so much improvement to make in the treatment of Myelodysplastic Syndrome. Some patients who are approaching blast percentages that are akin to leukemia will undergo chemotherapy and then as we mentioned stem cell transplant is an option for some patients. There are a small percentage of patients who have what's called hypocellular MDS meaning that when the pathologist looks at the bone marrow, there really aren't many cells there and some of those patients are thought to have suppression of their cells from the immune system and some of them will respond to various immunotherapies. Again, that's a minority of cases.

So for patients who have low risk MDS, for those who are interested in clinical trials and are past the state of observation and transfusion, some of the trials that are going on nationally are looking at an oral form of Azacitidine which would diminish trips to the doctor's office, which I'm sure would be welcome. Some groups are looking at lower doses of Azacitidine or

Decitabine to see if those will have similar effects. As I mentioned, there are still studies going on with Lenalidomide and you don't need to remember these names, but I put them up here because there are many different agents that are targeting genes or pathways that are thought to be apparent in the stem cells in Myelodysplastic Syndrome and various institutions throughout the country have some of these available. Some of the things that are being looked at on an investigational level in high risk MDS are, again, combinations of things like Vidaza and Lenalidomide. Drugs that, again, inhibit or disinhibit DNA replication that are called HDAC inhibitors like Panobinostat are being looked at in conjunction with Azacitidine and some groups are combining other types of chemotherapy. Example I gave here is a drug called Clofarabine and one called low dose Cytarabine with agents like Decitabine or Vidaza to see if that will improve response rates.

Here at the University of Rochester, the two clinical trials that we have open in Myelodysplastic Syndrome right now are both national studies that many different groups are participating in. As I mentioned for the low risk MDS groups, we're looking at Lenalidomide versus Lenalidomide with Erythropoietin to see if this will improve blood counts in these low risk MDS patients and then in a high risk patients, there's a study that's looking at Azacitidine by itself in a third of the patients, Azacitidine with Lenalidomide in another third and then Azacitidine with Vorinostat which is another one of those so called HDAC inhibitors in another group and this is including high risk MDS and CMML but it's need of treatment. This is the chronic meylomonocytic leukemia that we mentioned. It comes under the MDS umbrella.

If a patient has been on one of these standard agents that's approved by the FDA and then has progression, many of us at that point particularly for patients who aren't candidates for stem cell transplant would highly encourage participation in a clinical trial and this is just, again, a list of some of those that are available nationally. There's a drug who (inaudible 55:28) that inhibits multiple pathways within the MDS cell that is under investigation. Again, combining chemotherapy drugs in low doses to improve MDS and incorporating some of these titated agents into the treatment on an ontarium have all been proposed and are in fact being looked at.

So just to summarize, again, I want to emphasize to you that when we talked about therapy in MDS, we really have to select a therapy that's best suited to the individual. We're certainly going to take into account all of those prognostic factors that we talked about, the classification of the MDS, the severity of the blood counts and the abnormalities that are present in the chromosomes, but we have to select therapy that's going to be best for the individual. We want to minimize toxicity. We want to, obviously, improve blood counts without having complications from transfusions. We want to prevent infections that can occur due to low white blood cell counts and we, obviously, want to improve quality of life and prolong the survival and with that I'll turn it back over to the MDS group. So any questions that anyone has at this point? Because I know that's a lot of information, but hopefully it gives you an overview or something to start with as we think about MDS.

Q1: With the CMM and outline, you talked about two drugs being put together to supposedly help therapies to help with the CM (inaudible 57:30). Does… What do I want to say? You call it clinical trials. At what point would you be able to participate in a clinical trial of that sort?

Jane Liesveld, MD: That's a good question. Most of these will have criteria meaning that the disease is of severity that it requires treatment. Meaning that someone has already had, for example, a transfusion need or has a certain blast percentage in the bone marrow that would indicate that they could benefit from treatment, so and they're also cut offs, for example, if the platelet count is below a certain number and so there's a whole array of criteria that determine with a patient would be able to go on those studies. So, they're basically designed for patients who are in need of some sort of treatment and aren't just on an observation (inaudible 58:30) at that point. Yes?

Q2: Just a very general question. There was a lot of information in those slides. Are they available anywhere that we can…?

Jane Liesveld, MD: Yeah. Most of these are from published literature…

Q2: I saw that.

Jane Liesveld, MD: … and I think that in some of the materials that you've been given and also on the MDS Foundation website, many of those slides that have to do with the prognostic scoring systems are all available. In fact, I took those right from their website. So, most of those are available in some form and if there's anything in particular you want, I'd be happy to E-mail it to you. Again, these are copyrighted to our knowledge.

Q2: Thank you.

Emily Knight, RN: So everyone got a binder when they came in and the MDS Foundation has put together what's called the *Building Blocks of Hope* which is a guide for patients and caregivers for living with MDS. The International Leadership Board put this together and has provided it for patients and families. It's a good tool to have and we'll be going through that today kind of looking through the binder, how to use it, what's useful, what's helpful. So again, we'll keep this informal. If there's any questions as we go through it, just let me know.

It's a global print and online patient advocacy initiative providing personalized education 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 the beauty of the night sky over the sand swept desert and the stunning mountain ranges. The colors are meant to represent welcoming, warmth, stability, healing passion and protection. They form the base of the *Building Blocks of Hope* logo constructed in a wavelike pattern that indicates the fluidity of life, health and illness. The single red band which

continues up the plant symbolizes strength and improvement in bone marrow function with the idea of hope for the future and extension of life as emulated in the sprouting plant. So, that's what the *Building Blocks of Hope* is. This is the Nurse Leadership Board that has put together the *Building Blocks of Hope* and as you can see, there're nurses from the US and across the country participated in this.

So, what the *Building Blocks of Hope* does or what it's meant to do is answer common questions that you might have about MDS. So, understanding a diagnosis, how it is diagnosed, what are your treatment options, what are the common side effects of the treatment, what can be done to control those side effects, what new treatments are on the horizon. It talks about the consequences of blood transfusions, should you receive iron chelation therapy if you've had several blood transfusions. If you're in a position for a bone marrow transplant, how do you select a transplant center and then most importantly how do you keep yourself healthy because if you have MDS, you know that your blood counts may be low, you may immunocompromised. How do you just stay health?

So, Tools and Strategies for Success. We'll explore the *Building Blocks of Hope* to help you better understand the disease. Know your IPSS or now your IPSS-R risk category. Be aware and able to ask questions about your treatment options. What would the treatment schedule be like? Possible side effects of those treatments and then strategies for managing those side effects and then also with treatment you have to consider your lifestyle. How frequently are you going to be going to the clinic? Are you going to be needing transfusions? How frequent is the treatment? Be able to ask for help. It's important… a lot of you came with family. So, it's a family or friend, it's good to have a support system because you need that second set of ears to take in the information because it can be a lot and then just becoming a partner in your MDS journey. Building Your MDS {lan. Tracking your progress. All of that is in the binder and we will definitely go through that.

So, this is a lot of review. We won't go through all the slides because we just went through that with the previous presentation on what MDS is. We know it's a blood or bone marrow cancer. I'll flip through these real quick and we'll get to the *Building Blocks of Hope*. The one thing that I will stop and point out that in our clinic and what we emphasize to our patients is that if you're requiring treatment for your MDS, whatever treatment that may be, any treatment for MDS requires time to work. So, it's important to remember that even though you start your treatment, your blood counts likely may get worse before they get better. So if you're starting treatment with Vidaza… As the Vidaza or Azacitidine starts working, it cleans out the bone marrow so the blood counts can drop. So before you will see your response, it can take four to six months before you see that response and that's what these slides show here. So, it's showing the bone marrow being cleaned out and then as you respond the blood counts will recover and you can be weaned from that supportive care.

So, here's the slides on the *Building Blocks of Hope* and becoming in your care and building your MDS plan. So, tab one in the binder is Understanding MDS and it comes with a complete description of the disease process and answers common questions that you may have and then tab two is Seeking Treatment. The treatment of MDS can vary based on the type that you have and how severe it is. This section provides details about various approaches to treatment. So, if you go through that and then tab three is Quick Tips. The Quick Tips offered in this section include guidelines for monitoring and managing your symptoms and the symptoms range from everything from the low blood counts with fatigue, anemia to anxiety, depression. So, it goes through any symptoms that you may be having and helpful tips on how to manage that and then tab four is Iron Overload, possible outcome of repeated red blood cell transfusions. So, tab four talks about that and then tab five is My MDS Plan, understanding the diagnosis will help you and your caregiver take an active part in your individualized treatment plan. The My MDS Plan provides several tools that allow you to track and manage your journey. If you go to that tab in the binder what is helpful for people and what you can do. Before you start using it, make some additional copies. If you like to keep track of your blood counts, it's a nice sheet there that you can make extra copies and keep those and keep a running record of your blood counts and transfusions and medications and then tab six just talks about the MDS Foundation. It's an internationally public support organization dedicated to serving MDS patients, caregivers and professionals that are working to improve the lives of patients with MDS and provide a number of resources which support the *Building Blocks of Hope*. So, there's an online and patient advocate support… I don't know if you guys have been to the MDS website, but this *Building Blocks of Hope* is all online as well. So, I'd encourage you if you're Internet savvy to get on the website and just check it out. Explore what it has to offer.

So, lots of people to acknowledge. Contributors. There's patients and caregivers who contributed to it, the board member, the staff at the MDS Foundation. I don't know if you've had a chance to look at it or if you've been online before, but it is a really nice tool that can be used and helpful to understand and track your disease. I don't know if a lot of you are going for frequent lab tests or if you're on treatment, but it can be a very helpful tool for patients and family members. Did anyone have questions about the binder specifically or about MDS? It is a lot of information, but it's helpful. So, if you have any questions while looking through it let me know. After lunch we're going to go through kind of talk about quality of life, living with MDS, how it impacts your day to day and I think lunch isn't coming for like 10 – 15 minutes. So, just let me know if you have any questions.

Q3: One. Let everybody introduce themselves.

Emily Knight, RN: You can go around if everyone is comfortable. If you're comfortable with it, you can go around and introduce and say if you're the patient or if you're on treatment or share whatever you want to share.

Q3: You want to start, Bryan?

Bryan: My name is Brian coming Mississauga, Ontario. My mom was recently diagnosed with MDS and also I just found out my uncle, actually my mom's younger brother, was also diagnosed about two months ago. So, quite a (inaudible 1:10:23) for me because I never heard of MDS before until this March. My friend's wife passed away because (inaudible 1:10:34) MDS last year and (inaudible 1:10:39), but never heard of this, so I didn't try to finding much more information about that and also we… my mom hadn't really start treatment and also I would like to ask doctor about a couple questions later on.

Rudy: My name's Rudy G. I'm a resident of Rochester. I'm not the patient. It's my daughter who lives in Florida and she had had double mastectomy in 2008 and got 4 rounds of chemo after that and the follow-up blood work, blood work was bad. So, they started to do more tests and did a bone marrow and, well, the pathologist then did not see signs of MDS. They did see an abnormal chromosome. So, she went Moffitt Cancer Center in Tampa, Dr. West. They repeated the bone marrow studies and he did see MDS. That's the bad news. Also saw the chromosome abnormality. However, the good news is it's not an abnormality, a chromosome abnormality that's often associated with MDS. She's had it since birth which a translocation and apparently it has nothing to do with the MDS. Also good news. It's at a very early stage, very mild. She's on the young side. She's 58 now. She was diagnosed 2 years ago. It doesn't seem to be progressing. She's not had to have any treatment up to this point. However, it's one of these watch and wait sorts of things. If it does progress, I'd like to know more about it which we can be supportive. So, that's what I'm here to find out what I can about it and relay whatever is useful to Suzanne and keep hoping.

Q4: Actually, we saw that… I just did too much talking and I'm one of the… I'm here at Strong and I do take care of mostly patients who have Myelodysplastic Syndrome, leukemia and I also do bone marrow transplant.

Dawn: I'm Dawn D. I'm a friend of Sharon's, here to support her today.

Sharon: I'm Sharon D. I have CMML. So, I'm very interested in anything to do with AML. I've had it for three years. I still continue to be in watch and wait phase and so far I've had no treatment. This knowledge that we have received today is (END OF AUDIO)