

Speakers:

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Suman Kambhampati, MD: The purpose of today's talk is basically to give you sort of an overview of what Myelodysplastic Syndrome, or MDS, is from a patient's perspective and also to give you some light on some of the new trends that are occurring in MDS especially with the drug development and I'll also share with you some of the local trials here that we are doing based on some new data and then at the end of the talk, I'm happy to take questions. I do have a confession to make and that is I have to take my daughter for a soccer game after this. So, please I apologize if I leave after my talk, but that's my commitment to her. So, I apologize again, but I do... I'm open to any questions anytime and you guys have my contact to call or E-mail me.

So, the title of the talk is "Optimizing Patient Outcomes." These slides were actually put together by a number of experts and these are sponsored by the clinical care options and I do want to confess... I do want to acknowledge some of the experts who were behind this slides. One of them is a good friend of mine and we trained together in Chicago, Dr. Verma, and I extend my gratitude to him for sending some of the slides for this presentation.

So, this is the overview of the program today. We'll talk about MDS classification and share some data on cytogenetics or also known or chromosomal anomalies and then talk a little bit about the options for lower risk MDS. I'll explain to you today what it means and the difference between lower risk MDS and higher risk MDS. We'll talk about some of the new treatment options for high risk MDS and lastly also discuss some supportive care measures in patients with Myelodysplastic Syndrome.

So, topic one is how is MDS classified? MDS is basically a hodgepodge of various diseases that get termed as Myelodysplastic Syndrome and how do we distinguish different diseases in MDS and what is the significance of the chromosomal study.

So, the overview slide here covers all the important aspects of MDS. MDS is a malignant hematopoietic disorder. Some patients ask me if I have a cancer and my answer usually is yes, this is cancer. Prior to... In the 1960s when MDS was not recognized as a cancer, the incidence of MDS in the United States was 60 cases and now we know that now that we have started coding this cases as cancers we have a true measure of the overall incidence and prevalence of this disease.

So, it's characterized by bone marrow failure. That's one of the pathognomonic findings of MDS. The bone marrow stops producing blood and that results in low blood counts and when the blood counts go low, patients are susceptible to complications such as bleeding due to low platelets, fatigue due to anemia and infections due to low white cell count. Anemia, however, is the most common presentations. The majority patients present with anemia and this is actually a

sign that should prompt referral to a hematologist by the general care providers and if you're not getting a referral, you can actually contact the specialist directly. The key finding of this anemia is that these cells are actually bigger. They're large in size and one of the reports in the CBC measures the size of the red cells. It's called MCV. So if you have anemia with elevated MCV, then you should be evaluated by a hematologist. The hematologist then would do a bone marrow biopsy to find out why a patient is anemic and without a bone marrow biopsy, it's possible to make a diagnosis of MDS, but I'll tell you why bone marrow is an important test for the diagnosis of MDS. So by bone marrow, the appearance would be abnormal. Under the microscope these cells look abnormal and some of the cells are highlighted here and basically you can take my word that these are abnormal cells based on their appearance. They appear larger in size compared to normal cells and sometimes there is an increased clone or leukemia clone and the maturation, the cells they mature within the bone marrow from early precursor cells to mature cells and that whole maturation process is apparent in MDS. So, the factory of blood production is impaired in MDS and then in patients who have a higher burden of leukemia in their bone marrow they have the risk of progressing into acute myeloid leukemia which is a lethal disease and what makes it even more lethal in patients who have MDS is because the treatment resolves or the treatment outcomes are very poor for patients who present with AML that evolve from the preexisting MDS.

So as I said before in the '60s they were just a handful of cases. Now the overall incidence is anywhere from 3.7 to 5 cases per 100,000. About 10,000 new cases are diagnosed in the United States. However, this is still an underdiagnosed disease. Many patients actually do not get the referrals in a timely manner for anemia, low blood counts. So, the overall estimate is that about 37,000 to 48,000 patients are probably living with Myelodysplastic Syndrome. The median age is 70 years. So, patients often ask me why did I get this disease? The answer is we do not know why, but it's likely because of your age. It's a disease that affects the elderly. The median age being 70. The incidence rises with advancing years. So, about 75, for example, the incidence is 34 to 50 cases per 100,000 and this is important to remember because there's almost 10 times the number of cases that are diagnosed in patients who are 75 or above and, again, this is something that I definitely emphasize to all my trainees and to my referral docs. This is well illustrated in this slide and you can see that with age, 50 to 59, the incidence is about 2.5 cases per 100,000; 60 to 69, 9 cases per 100,000. It goes up substantially between 70 to 79 and about 80 almost 50 cases per 100,000. So anemia, low blood counts in this age group should be investigated.

So, the most common presentation as I said before is cytopenia also known as low blood counts. Diagnosis requires a blood examination. So anytime a patient walks in, we look at their peripheral smear. A CBC should be done and the hematologist or the pathologist would then look at the blood smear and that evaluation or that basic evaluation then prompts a bone marrow biopsy and aspirate and why is it important? Because we can actually measure the chromosomes, the structure of chromosomes by doing a bone marrow biopsy because to measure chromosomes we need to capture, we need to study the progenitor cells, the early phase cells, which are usually absent in blood. So, that's why we depend on a bone marrow aspirate to capture those early

phase cells and we incubate them. We grow them in a culture dish and then we look at their chromosomes and this is one of the vital tests that's often not done. That's because bone marrow, there's reluctance in doing bone marrow aspirate in biopsy. I find it very difficult to accept a diagnosis of MDS without a proper bone marrow aspirate biopsy and cytogenetics and if patients come to me for an opinion, I basically tell them that without those three tests it's impossible for me to make an intelligent recommendation.

So, for diagnosis we require demonstration of dysplastic or abnormal features in one or more cell line and this is the complicated schema of myelodysplastic classification proposed by the World Health Organization in 2008. A couple of things I want to point out. One is that you can see there are different terms all that come under the diagnosis of MDS. If you have one lineage involvement then it's known as unilineage dysplasia. If there are multiple lineage or multiple low blood counts then it's known as multilineage dysplasia. There is a very specific entity called a ring sideroblasts which is defined by the appearance of red cells or precursor red cells under the microscope where the iron incorporation into hemoglobin synthesis is impaired. So, that leads to accumulation of iron in these cells and that has a very categoristic appearance. So, that's known as RARS, refractory anemia with ring sideroblasts. This is actually an important entity to recognize now because of some of the new therapies that are coming out and those tend to have very, very good response in patients who have RARS. Once the leukemia clone starts expanding, we divide MDS into two categories, one and two. Patients who have about five to 10 percent leukemia cells in their bone marrow are known refractory anemia with excess blasts type 1 and once it exceeds 10 percent, 11 to 20 percent range is termed RAEB Type 2.

This is a very important entity to recognize. Again, this is why we need a bone marrow biopsy because the chromosome five, once it gets affected, once the long arm of chromosome five is affected. So, we have two arms in a chromosome, short arm and a long arm and in 5Q the long arm of chromosome five is deleted and once that is missing a lot of key genes that are involved in blood production are impaired. So, those genes are missing and that's what leads to anemia and low blood counts. There is more and more recognition of childhood myelodysplastic syndrome. So, even children can present with low blood counts and they should be investigated for MDS and there is this rare but an increasingly recognizable entity where the bone marrow blasts are less than five percent in bone marrow, but in blood the blasts are greater than two... equal to two. So, that's again an entity that should be recognized as MDS even in the absence of leukemia in bone marrow.

This is a very complicated slide but very simplistically speaking the chromosome analysis is done by an expert pathologist and then they figure out whether any parts of the chromosomes are missing. When some parts of the chromosomes are missing that's... it's given a minus number. So, that means that part of the chromosome is missing. When there is a translocation meaning that some of the genetic elements are translocated from one chromosome to the other chromosome. That's known as balanced translocation. So, you see these numbers like 1116, 321. That means that there's been some genetic transfer or material transfer between the two parts...

between two chromosomes and once patients have greater than equal to three chromosomal changes, that's termed as complex karyotype or complex anomaly. So, these are some of the things that we look at very, very carefully and hence a bone marrow biopsy is very essential to find out whether the patients have any of these chromosomal changes.

Dr. Greenberg, one of the pioneers in MDS research and therapy advances came up with this very simple classification in 1997 when I was still in training and it basically divides MDS into four different categories and the classification is dependent on bone marrow blasts. So, hence a bone marrow biopsy is needed. Karyotype also known as chromosome analysis. Again, that's why we need a bone marrow biopsy and the cytopenias can be detected or can be calculated by just blood tests. So, that's why we need a blood analysis and also a bone marrow biopsy. You divide patients into Low risk, Intermediate 1, Intermediate 2 and High. Now, look at this survival for Intermediate high risk MDS. It's four months. So in patients who have bad chromosome structures and increased number of leukemia burden in their bone marrow, 11 to 20 percent or 21 to 30 percent. Their survival is actually worse than a lung cancer patient. Lung cancer patients who have stage four disease often live about a year or longer. Patients who have high risk MDS live for about four months. That's an important entity to recognize and I talk to you about low risk and high risk MDS. Patients who have Low or Intermediate 1 group IPSS are categorized as low risk MDS. Those who have Intermediate 2 or High given their short lifespan are categorized as high risk MDS. So, that's how we differentiate low versus high risk. Again, the key points are bone marrow blasts, chromosome analysis and blood... the number of low blood counts. So, those are the three elements used to classify MDS.

More recently, the Germans and the Consortium of US Investigators have found out that these chromosomal analysis is getting more and more sophisticated. So now, they have categorized chromosomes that are very good associated with very good prognosis, good prognosis, intermediate, poor and very poor. So again, this should again emphasize the need for bone marrow testing to read chromosomes and in doing this analysis they have further divided in MDS into different categories. They have looked at cytogenetics or chromosomes. They have looked at the bone marrow blasts and in this new classification the bone marrow blasts are further categorized. So, you get points... You get no points if it's less than equal to two percent in bone marrow. It's greater than equal to two or less than five, you get one point and so on. So, points are granted for patients who have more number of leukemia cells in their bone marrow. Depending on the degree of anemias or hemoglobin, it gives us the degree of anemia. If it's less than eight, you get more points. If it's greater than about 10, you get zero points. Platelets, again, these are the cells that are important to clot, make the blood clot and if it's less than 50 you get more points. If it's greater than 100 you get no points and the neutrophil count. These are the cells that are the fighter cells. They help us fight off an infection. If it's less than 800, you get .5 points. If it's about 800, you get zero points. So, this is the analysis that we use to divide MDS into different categories and under this new classification or revised IPSS classification, we have five different categories of MDS, very low, when the score is less than equal to 1.5; low when it's between 1.5 to 3; when greater than 3 to 4.5 intermediate; greater than 4.5 to 6 high and

greater than six very high. So, this is how it's further refined based on new data on cytogenetics and also the degree or depth of low blood counts.

So, this is how new plots look. In patients who have very low risk MDS, their median survival is about 8.8 years. Remember the previous classification gave them a median survival of about five years, five to six years. So, this further refines patients into different categories and low risk MDS has 5.3 years; intermediate, 3 years, high risk, 1.6 years and very high risk, this one here, eight months. Again, helping us understand the poor prognosis associated with blood counts, number of blasts in bone marrow, cytogenetics or chromosome analysis and the depth of and the degree of cytopenias or low blood counts.

So, let's talk a little bit about the low risk MDS. This is how we approach low risk MDS. I want to point out that this slide was actually made in 2013, but there's not been much change made to the algorithm of Low to Intermediate 1 MDS. However, this is soon going to change with some often new therapeutics that are coming in the pipeline. So, the first basic thing we do is we find out if there are any treatable causes of anemia like B12 deficiency, folate deficiency, alcohol or other toxins. So, that's the first basic analysis. Everything can be tested by blood levels and in patients who have transfusion requirements if they're getting transfused for anemia then we try to divide them into three categories. Again, I want to point out this deletion 5Q which is defined by long arm chromosome... absence of long arm of chromosome 5, deletion 5Q. If patients have that, our first drug of choice Lenalidomide also known as Revlimid and it's an oral pill. If they fail this pill then we move on to the IV or other forms of chemotherapy or preferably a clinical trial. Our preference here is to offer them clinical trials and there's another blood test which measures the degree of erythropoietin. This is a hormone that's produced by the kidneys. When patients get anemic, the erythropoietin levels should go up. However in a lot of MDS patients, these levels stay low and when they're low or defined as less than 500 and if the transfusion burden for a patient is less or low also known as less than two units per month then our approach is to start them on growth factors. ESA is known as erythropoietin stimulating agent, also known as Procrit. The TV ads usually come as Procrit. So, this hormone along with a growth or a granular side stimulating hormone which stimulates the white cells can be used to address the anemia. So, this is our first approach. Measure the erythropoietin level, evaluate the transfusion burden and if they have low transfusion burden, find out if they will respond to erythropoietin first which is a very simple treatment. Patients often self-administer that patient. At the VA, we actually ship the drug directly to the patients for self-administration at their home. At the university, however, they have to come here which is a pharmacoeconomic burden, but nonetheless that's how the systems are and then in patients who fail this treatment we find out if immunosuppressive therapy would be useful. There are certain features that predict, that help predict response to immunosuppressive therapy and that's, again, defined here less than 60 years of age. So if patients are young, they tend to respond better to immunosuppressive therapy. If their bone marrow is less... if it less cellular meaning that the number of cells under the microscope are less then that, again, is a good predictor for immune suppressive therapy success and these other parameters are still under question, but we look at age and the bone marrow

cellularity in patients who are young and if they are young then we move towards immunosuppressive therapy which is given as oral or IV and if those work we continue them on immunosuppressive therapy for a long time. If that doesn't work then our next choice becomes Azacitidine also known as Vidaza, Dacogen or Lenalidomide for a clinical trial.

So, I'm going to talk a little bit about these drugs and then in patients who have serum erythropoietin level, again, this is a blood test. They can look at the blood test levels of erythropoietin and if these are high, greater than 500 and patients who have high transfusion burden of two or more red cells per month those patients are very unlikely to respond to these growth factors. So, we look at other options either immunosuppressive therapy or more traditional types of chemotherapy or a clinical trial. So, this is all of our schema for Low and Intermediate 1 MDS. Erythropoietin also known as Procrit or Aranesp has a response rate of about 16 to 20 percent. The predictors for response are serum EPO level of less than 500. If patients have a non-RARS, so this is known as a refractory anemia with ring sideroblasts. Ring sideroblasts, as I said before, are the cells that have impaired iron incorporation. So if they have a non-RARS type of MDS and if they lack high transfusion burden history then these patients are ideally suited to start Procrit or growth factor therapy and the response rates often go up to about 40 percent when we combine Procrit and GCSF together. The approach usually is to start with Procrit or erythropoietin alone first in patients who do not respond then we add GCSF and this combination actually works quite well in the refractory anemia with ring sideroblasts which is often resistant to Procrit alone.

What about this pill called Lenalidomide? What is the role of Lenalidomide in MDS? So, Lenalidomide is a derivative of Thalidomide. Thalidomide gained a lot of attention in the '60s due to birth defects and so this is an analog or a... I would say a modern version of Thalidomide and it's approved for Low or Intermediate 1 MDS that's associated with deletion 5. Again, chromosome 5, long arm of chromosome 5 is missing and even if there are additional cytogenetic or chromosomal changes, it does not matter. These patients should be treated with Lenalidomide. This is the pivotal trial that led to the approval of Lenalidomide. This was done in United States and also other countries led by Dr. Alan List and this the key criteria for enrollment was Low or Intermediate 1 or low risk MDS, patients who had that deletion 5Q, those who had a transfusion burden of greater than two for eight weeks, two red cells or transfusions per eight weeks, platelet count greater than 50,000 and ANC or neutrophil count greater than 500. They randomized to two arms, 10 milligrams daily, 10 milligrams for 21 days, one week off. Patients who responded were continued and patients who did not respond were taken off the study. The key end point, primary end point, for this study was transfusion independence meaning no need for any transfusions during the study phase and there were other secondary endpoints, too but the primary endpoint was transfusion independence.

These are the results. Patients who... Almost 70 percent of patients achieved erythroid response or hemoglobin response and look at this numbers. The median hemoglobin increase was five grams. So, if they're about seven grams before the treatment they went up to 12 grams after the

treatment and within one month of treatment, 4.6 weeks, within one month of treatment these patients had a hemoglobin response and most importantly the duration of response was very long lasting, over two years. The very key... one of the very key findings of this study was that the chromosome that lead to the disease, deletion 5Q was undetectable after a few months of treatment. So, almost 45 percent had complete cytogenetic or chromosome response and about 73 percent had complete cytogenetic response plus also changes in other chromosomes. If there are other chromosomes, those also got better. So, this was one of the key landmark advances in MDS which introduced the term ‘targeted therapy’ meaning you find a target, you give a pill or treatment to get rid of that underlying factor and this was a the proof that targeted therapy could be used in MDS. So based on this data, Lenalidomide or Revlimid was approved for 5Q- MDS for patients with Low or Intermediate 1 or low risk MDS.

More recently, last year the French and consortium of many investigator presented this data on Lenalidomide versus placebo, sugar pill, in low risk MDS, but patients who did not have that 5Q deletion. So, these patients did not have the 5Q deletion in which Lenalidomide is not yet approved. So the clinical trial looked at five non-5Q patients with low risk MDS. Again, the same... almost the same parameters for inclusion except that these patients did not have deletion 5Q. They were all transfusion dependent and they were not responding to Procrit or ESA, erythropoietin stimulating agent. They were randomized to 10 milligrams of Lenalidomide every day versus a placebo and at 24 weeks they looked at response criteria measured by RBC or red cell transfusion independence that lasted for about eight weeks or equal to eight weeks. If they did not have that criteria then they were taken off the study. If they met that criteria, they were continued for the long term follow up.

So, the results are here. If you remember in 5Q, the results... the erythroid responses were in the 60 to 70 percent range. Here the results are much attenuated. Thirty percent... 26 to 30 percent responses and in placebo arm only about 2.5 percent, so clearly giving a signal that Lenalidomide could be effective for non5Q low risk MDS. The great thing about this disease is... about this treatment is that the majority of responses are seen within 16 weeks or four cycles of treatment, which is again different from the 5Q MDS because in 5Q the responses were seen at four weeks, the majority of responses. Here, at about at the end of one cycle or four weeks about 37 percent responses, but there was an incremental increase in the response with every cycle. Ninety percent at four cycles.

One of the interesting features of this study was there were certain parameters that actually predict response to Lenalidomide in non-5Q MDS. So, females responded better compared to male patients. Patients who had previously treated for MDS, they responded better compared to those who did not receive any therapy and if they had low transfusion burden they were likely to respond better compared to patients who had high transfusion burden. So, the low was defined as less than four units of red cells in a month and high was defined as greater than four units of red cells in a month. Furthermore, if the patients who were exposed Procrit or erythropoietin stimulating agents they were likely to respond better than those patients who were not exposed to

ESA and if their serum erythropoietin level was less than 500, they were more likely to respond. So, these are some of the factors that we can look into in clinics just by looking at a patient by history and by blood level and predict how they're going to respond to Lenalidomide.

So, the summary of this abstract that was presented is here. Twenty six responses in low risk MDS and the median duration of response was about 32 weeks. Ninety percent of them responded within 16 weeks of treatment and the overall safety data is consistent with what's been already reported with Lenalidomide in 5Q MDS and also in multiple myeloma.

So, these phase three data support the use of Lenalidomide as a treatment for patients with low or intermediate 1 risk MDS without deletion 5Q who are unresponsive to erythropoietic stimulating agents. So, this is the summary or conclusion of that abstract and based on this data and other data we have been partnering with Dr. Varma at Einstein to do this phase two study of Lenalidomide and a rescue pill called Eltrombopag. So, the problem with Lenalidomide is that this pill causes the blood counts to go down and that's what makes it very difficult for patients to stay on this treatment for a long time and as I showed you before, it's the exposure time to Lenalidomide that's also important in non-5Q MDS. So in these patients the responses are seen slowly. So hence, it's important that we expose these patients to this drug as long as possible. So, what we have proposed in this trial is if patients drop their platelet counts then we're going to rescue them with pill called Eltrombopag which is approved for a condition called ITP that leads to low platelet count. So using that rescue strategy, our goal is to expose these patients to more Lenalidomide and we are hoping for better results with Lenalidomide in patients with Low or Intermediate 1 MDS. So, this study is open, accruing very well at both sites, Einstein and KU. Mayo Clinic is also one of the sites for this study.

So, this abstract that was presented last year got a lot of attention. This was presented by the Germans... German group and this compound called ACE-536 was studied in low or intermediate risk MDS and the results were absolutely amazing. So, this is basically a subcutaneous injection and it was given every three weeks for three months and they looked at different dose levels. These are the doses here and then patients were followed up and the one of the key things about this trial is that they actually looked at responses based on dose and also responses based on the transfusion burden. So, low transfusion burden or high transfusion burden patients it did not matter. They responded the same way in the right dose, .75 to 1.75. Forty percent response is something that's very remarkable in these really beat up, heavily transfused patient... independent patient. All patients responded about 40 percent.

Now, remember I talked to about targeted therapy in MDS. Lenalidomide was one of the first drugs to be proposed as a targeted therapy in 5Q MDS. We are getting a hint that this drug could be proposed as targeted therapy for patients who have ring sideroblasts, refractory anemia with ring sideroblasts. So, this is where the bone marrow diagnosis, again, comes to play. It's important to do bone marrow to find out if the patients have this category of MDS. We are seeing the first proof that mutational analysis, mutational analysis, not cytogenetics. This is

mutation analysis. We look at the genes that are involved in blood production and if they have a mutation in this gene called SF3B1, they're going to respond very nicely to this drug. Sixty-seven percent responses as compared to those who did not have that mutation. So, we are getting more and more proof that target therapy is feasible in MDS and furthermore not just the chromosomes or the appearance under the microscope even mutations can... presence or absence of mutations can predict response to these new drugs. So, this study... this drug is now being expanded. They're doing more clinical trials with this drug and a similar drug that's now being sponsored by Celgene and, again, the data looks very promising in ring sideroblast type of MDS and those with SF3B1 mutation.

Azacitidine is something that's used in low risk MDS and it's approved for all the subtypes of MDS. Based on data that was done in 2009 and earlier, there are different ways to give Azacitidine. You can do five days on, two days off, two days on again or five days on, two days on and then more five days at a lower dose or just five days alone. Regardless, it produces the same results. It doesn't matter whether you do it for five days, two days on, two days and then two days on again. The problem with Azacitidine is that it causes suppression of blood counts. So, that's a problem with this medicine and if you look at these numbers the treatment delays almost 68 percent of patients had treatment delays. So, it's better... I prefer just five days of Azacitidine in the low risk category of MDS because those patients had lower grade of hematological toxicities or low blood counts and also less treatment delays.

What about high risk MDS? High risk is defined as bad chromosomes and leukemia burden, increased leukemia burden, in bone marrow. This is how we look at... this is again, a very simplistic schema. If patients are a candidate for stem cell transplant, we go straight towards transplant after finding a matching donor. If there is no donor available then we go towards Aza nucleosides also known as Azacitidine or Decitabine. Those are the two drugs known as Aza nucleosides. Ideally however, we should always look for a clinical trial. So, our approach here is to look for a clinical trial. If there are none available, not a legible patient then we move towards Aza nucleoside.

Chromosomes, again, play a part here in making a decision for transplant. So in patients who have favorable chromosomes, we move towards transplant. If there are unfavorable especially frail patients then we choose to do medical therapies. There is an ongoing national clinical trial lead by the Bone Marrow Transplant Consortium, BMTCTN, and we happen to be one of the sites accruing for that trial which is looking at this exact same schema in a prospective fashion meaning that patients will be studied throughout the course of their treatments depending on their donor availability. So if there's a donor available, they'll get transplant. If there is no donor available then they'll get medical therapies and this study will look at the overall survival between transplant versus medical therapy depending on the donor availability or their eligibility for transplant.

How do we make a decision about transplant at diagnosis? This is very well summarized in this slide. If patients have high risk MDS, we prefer to offer them transplant at diagnosis because data shows that we can add to their lifespan by offering them early transplant. If they have low risk MDS, Low or Intermediate 1, it's better to offer transplant at progression. So, that's how we make a decision on when to do transplant, the timing of transplant based on the subtype MDS, Low or Intermediate High. Most of the data, however, comes from the era where all these FDA approved drugs were not available. Nonetheless, we still use this basic paradigm to make transplant decisions.

What about chemotherapy before transplant? Does it have any role? Does it make any meaningful difference? The bottom line is that there is no benefit for a chemotherapy prior to transplant. If there is a donor available, let's move forward with transplant. What about in patients who do not have a donor available in the form of a sibling donor or an unrelated donor. Then until we can get a good donor for that patient or identify a good donor for that patient, we offer them some form of bridging therapy either Azacitidine or Decitabine before transplant and this strategy has not shown to effect the donor engraftment. In fact, it speeds up donor engraftment. So in a way, we have shown the feasibility, but there is no robust data to propose either Azacitidine or Decitabine prior to transplant. So if their disease is controlled, we monitor them periodically with bone marrow biopsies or blood counts, but if their disease is growing and if transplant is going to be... if it's going to take some time then we offer them bridging therapy with Azacitidine or Decitabine. Again, I want to point out there's not a lot of evidence, but whatever evidence we have does not show that it's going to harm that patient in any way.

So, this is the trial that led to the adoption of Azacitidine at least in my practice as a front line choice for high risk MDS. The French looked at Azacitidine versus standard of care options including very complex chemotherapy and in this study they showed that Azacitidine actually was better in the overall survival of these patients. Twenty-four months for Azacitidine, about 15 months for other choices. So hence, I use Azacitidine as the front line choice for high risk MDS. Again, the problem with Azacitidine is that a lot of these patients end up dropping their blood count. So, we actually make the counts worse in the initial phases of treatment. They're low... Their neutrophils drop. The platelets drop. Anemia becomes a factor. They develop febrile or fevers due to low blood counts, fevers and many other complications. So, the bottom line is that these treatments not only suppress the cancer clone, but they also suppress the normal clones and hence they lead to low blood counts. So, one has to be vigilant for all these. So, we see these patients almost on a weekly basis in our clinics. At least on the first few rounds of treatment and if they do fine then we increase the duration to every two weeks or once a month, but in the initial phases of treatment you should see them at least once every week.

This is the other drug, Decitabine, that's also been approved for high risk MDS or MDS of any category and this drug, for me, is a second line option because the trial did not really show or did not meet the primary end point of overall survival benefits. So hence, I use Azacitidine. The other advantage of Azacitidine is it can be given as a shot as a subcutaneous injection. So, it's

much easier. It saves the chair time, much convenient for the patient. Of course, the skin rash and skin toxicity is a problem with Azacitidine, but most of the patients we can manage them with the proper injection techniques.

This study was presented last year in December in our society meeting. Very high impact study that looked at Azacitidine alone or Vidaza, Azacitidine plus Lenalidomide or Revlimid and Azacitidine plus a new pill, Vorinostat. The hypothesis was by combining these drugs we can get better results as compared to Azacitidine. So, this was the primary objective. Can we improve the responses compared to Azacitidine? The secondary responses were... objectives were overall survival, leukemia free survival and relapse free survival.

Millions of dollars spent on this trail. The summary is here. Azacitidine came out as the winner. There's no difference in overall response rate comparing Aza plus Lenalidomide or Aza plus Vorinostat to Aza alone. So, there's no difference. If you're getting Azacitidine then you're getting the standard of care. You're getting the best care that's available by scientific evidence. There was a hint that some subgroups may have benefited from the combination arms, but that's yet to be seen. We'll see the full evidence in the manuscript, but at the moment Azacitidine is still the standard of care. There was also some signal that the disease free survival might be better for one of the arms that involved Azacitidine and Vorinostat, but that data is not yet mature. We'll see in the manuscript how that pans out.

We were involved with this study which is an on time study sponsored actually I know MDS Foundation promoted this study very well looking at patients who failed Azacitidine or Decitabine which is a big problem. Once they fail then the options bleak. The outcomes are bleak. So, this study looked at patients who did not respond to Azacitidine or Decitabine in high risk MDS and I want to point out if you do nothing, just offer them blood products, the median survival is about four months. If you offer them a clinical trial, you can improve their median survival up to 13 months, up to a year. So, just offering a clinical trial helps the patients live longer and generally our goal is to get them to a transplant as soon as possible, but that's easier said than done. So therefore, we use the clinical trial as a bridge to transplant and the best outcomes are if you can get a donor and get them to transplant. So in this study that looked at this continuous infusion of this drug called Rigosertib versus best supportive care or a low dose chemotherapy, the overall survival no difference. So, this is the overall survival plot between the study arm and the supportive care, transfusion alone arm. No difference at all. 8.2 months, 5.9 months. This was not statistically significant and there was a hint though that in patients who had no response to Azacitidine or Decitabine. So in other words, four cycles or six cycles of treatment produced no improvement in their blood counts or their bone marrow. Those are termed as primary hypomethylating failures, hypomethylating agent failures. So, in those patients perhaps there is a hint that this drug is effective and based on this hint now they're doing the next phase of this clinical trial and we would be one of the sites involved with this study to look at the role of Rigosertib in patients who have no response whatsoever with hypomethylating agents.

So, the conclusions are summarized here. The endpoint overall survival did not reach statistical significance. It was 2.3 months, but again did not meet the level of significance. In patients who had hypomethylating agent failure, primary resistance to those drugs or patients who had a very high risk MDS or patients with certain cytogenetic changes perhaps there is a hint of benefit in overall survival using this drug, but again these studies will be done in the future to really see the true impact.

We here are looking at this pill called Pyrimethamine and if you followed the news about the drug prices Daraprim, Turing Pharmaceutical jacked up the drug, this generic drug which used to be \$5, \$13 to \$750. This is exactly the same drug believe it or not and in fact they have promised us that they will give us this drug for testing in MDS patients. This studies... the lab studies were done by Dr. Varma at Einstein and based on that we have designed this phase two study. Again, a collaboration between Einstein and KU to look at this pill, Daraprim or Pyrimethamine, and see how this effects patients who have failed Azacitidine and Decitabine. So, stay tuned. This is soon going to open at KU for patients who are failing other conventional drugs.

This is how the landscape looks. Oral Azacitidine or oral Vidaza is something that is intriguing. We just published the results this year. It looks intriguing. Future studies will be planned. Clofarabine is something that's very difficult to administer. MD Anderson folks have shown the feasibility with good responses, about 40 percent or so in my hands. In the patients I treat, I find that very difficult to use and there are a couple of other drugs. Rigosertib, I talked to you about that and this study, the next phase of this study will open soon. The other drugs are still very early and the data is promising but not ready yet for prime time.

What about the supportive care? How should we address the transfusion needs and the iron overload that's seen in these patients who become heavily transfusion dependent? The primary goal is to make the patients transfusion independent. If they get less blood products, they're likely going to live longer and that's exactly what's shown here in these graphs regardless of whether they have low risk or intermediate risk MDS. So, less blood transfusions make a difference, overall survival difference.

This is some of the tips that we use to find out which patients would benefit most for iron overload. MDS Foundation has its own criteria. The NCCN guidelines that are used has its own criteria. The bottom line is that if their transfusion requirement is greater than 20 or if they're needing two units per month for over a year which is about 24 units or so, it's probably a good idea to be evaluated for iron chelation and that's particularly import for patients who have low risk MDS, Low or Intermediate 1 MDS because these patients are going to live longer as compared to high risk MDS. So, it's important that we preserve their organ function and also make them candidates for allogeneic transplant down the line and iron chelation has shown that it can prolong the survival of these patients and also preserve the organ function.



So, I do want to acknowledge the families and patients all over the world who have contributed to this research. I mean, again, I pointed out in the beginning that 60 patients in 1960s were diagnosed with this disease. Now, there's more and more awareness of this disease and really without their commitment to these trials we'd still be in the Stone Age. MDS Foundation, you guys have been terrific in promoting awareness about this disease and all the new advances are thanks to the MDS Foundation and their efforts to involve more patients in clinical trials. The authors and scientists of all the work that I presented, the pharmaceutical companies also need to be lauded for these efforts because without them a lot of these drug development would be impossible in my opinion. (Participant), thank you for arranging everything meticulously and I have my numbers here. My E-mail is there, my card is with you guys. If you have any questions, feel free to reach out to me and thank you for being here. We appreciate it very much. So...

(Applause)