



Birmingham, Alabama Patient and Family Forum June 25, 2016 – Part 1 **Page 1 of 21**

Speakers:

Harry Erba, MD, PhD

Sara Tinsley, PhD, ARNP, AOCN

Audrey Hassan

Audrey Hassan: Hello, everyone, and welcome. I'm Audrey Hassan the patient liaison with the MDS Foundation and I don't know if you had the opportunity to meet Debra Murray from our office and on behalf of the MDS Foundation we welcome you here today. It is an honor and pleasure to have as our guest speakers today Dr. Harry Erba from the University of Alabama at Birmingham and Dr. Sara Tinsley from Moffett Cancer Center in Tampa.

Immediately following this program we are going to have a talk on iron overload. So, you're more than welcome to stay after our program is over. We're happy to announce the Dr. Stuart Goldberg from the University of Hackensack in New Jersey is here as well. So, he'll be presenting that program. So, please stay if this is something that you'd like to attend.

Without further ado, I think we should get our program started. I'd like to introduce Dr. Harry Erba. Please help me in welcoming him.

(Applause)

Harry Erba, MD, PhD: Thanks and thanks for coming out this morning.

I really encourage you to stay for lunch not because I've seen what's on the menu, but I know that my good friend Stuart is speaking and anything I say wrong he will correct. So, I'll leave and he'll set the record straight.

So, let's get started. So, we're going to talk about the Myelodysplastic Syndromes and we're going to talk about how people present with this disease, how it's classified and get to treatment options that we have now and maybe in the future. So, I have a lot that I'm going to try to cover during this next hour, but we can't understand the myelodysplastic syndromes unless you understand what's the normal production of your blood. This tissue is amazing. It's amazing what our bodies do. So, what you're looking at here are photomicrographs of peripheral blood smear. So, when we take a purple topped tube from you and we smear out a little drop down the slide and stain it this is what we're looking at under the microscope and all of those brownish orange circles are the red blood cells and you can see they're the most numerous cells in there. The arrows are pointing to tiny things. These tiny things are the platelets. Platelets clot your blood. That's what they're part of. There's also proteins in the serum around the red blood cells that cooperate with the platelets in clotting the blood. So, that's what the platelets do. They're usually about one-third to one-quarter the size of a red blood cell. They look purple like that because they have a lot of little granules in them that have things that help form the clot and then there are different types of white blood cells. One thing that confuses my patients quite often is

we start talking about white cells and then we talk about neutrophils and what is all that about. Well, white blood cells are basically the blood cells that have nuclei, still have their DNA and there are several types of them. Let me point out that first though the red cells don't have nuclei. They are just packets of hemoglobin that are going to carry oxygen around your body. That is their job. Platelets don't have nuclei. They're just packets of these chemicals that help form a clot, but the white blood cells what they all have in common is they still have their DNA and they show up on the peripheral blood smear as having nuclei and there are different types and they do different things. So, this cell over here is the neutrophil and we recognize it because it's got salmon colored granules in it that have enzymes in it that kill bacteria and fungi and the nucleus has this funny shape that looked like sausage links that have been just stuffed into the cell. So, those are called polymorphonuclear segmented neutrophils or neutrophils and when we measure the absolute number of those we call it your absolute neutrophil count. So, we often talk about your white count, but we talk about the neutrophil count and the neutrophil count needs to be... should be over 500 to protect us from infection. So, in every microliter of blood there should be at least 500 of those.

There are other types of white cells though like these cells here. This is a lymphocyte part of our immune system that can be B cells or T cells and they fight off infection typically viral infections. Now, what you need to know about all of these cells is that they have a finite lifespan in the blood. So, you're not born with these on day one and they stay with you until the end of your life. They are constantly being replaced. Now, red cells and platelets are constantly being replaced because they don't have nuclei to actually make new proteins as they wear out in the cells. So, they get old and they get killed in the body, just taken out. The spleen is the organ that typically does that. Red cells have a life span of about three to four months. Platelets have a lifespan of about a week and neutrophils although they have a nucleus in them and could make more proteins don't. All of the genes in that cell are pretty much silenced and these cells they last maybe less than a day in the blood and remember they do nothing in the blood. If a bacterial cell has gotten into your bloodstream, you're going to be really, really sick. The job of the neutrophil is to go to our outer defenses and keep bacteria and fungi from getting into the body. So, they just use the blood stream to get to the tissues. So, the white cells use the blood to get into your nasal passages, your throat, your lungs, your GI tract, your skin, all of the places where our body meets the external dirty world. That's their job.

So, they only last about a day as I said. So, obviously, you need to keep producing those cells and the way we do that is in the bone marrow. Now when we're in our mom's womb, the blood is made in the liver and spleen, but it gets moved over to the bone marrow and what you're looking at here is a photomicrograph of a bone marrow section. How many of you have had bone marrow biopsies? This is what you are giving your bone marrow for for us to section it, to cut it and stain it and look at how the bone marrow's working because that's where those blood cells are made and what you see here are these pink things are just little bony trabecula we call them spicules when we see it in the aspirate. This is the core biopsy. All of the purple stuff are blood forming cells and all of the white circles are fat and the cellularity of your bone marrow typically

for 50 year old would be about 50 percent. For an 80 year old it would be about 20 percent. Cellularity means the amount in your bone marrow that has blood forming elements in it and the rest will be fat. Now at a higher magnification you start to see that not all of these purple cells and those in the nuclei look the same. The things that can stand out most easily are these cube cells. This one and this one and those are called megakaryocytes. Those are the cells that make platelets and that's what they should look like. They're big and their nuclei have all of these funny shapes. One big nucleus with a funny shape to it.

There are other cells in here that are making red blood cells and Stuart and I would probably pick these cells out here as the ones making red blood cells because the nuclei are really dark and round and they kind of hang together and then there are other cells scattered through here that are making granulocytes that have a more oblong and segmented nuclear shapes like these here. They're all mixed and jumbled up together and they're not just growing in a soup. They're growing on a tissue we call it the bone marrow stroma that has important signals that tell these cells how to grow.

So, we depend on the bone marrow to make one percent of our red blood cells a day because one percent of our red blood cells die every day and we depend on the bone marrow to make platelets and white cells.

The disease Myelodysplastic Syndrome is a disease where our bone marrow cannot do this appropriately or efficiently. That's what Myelodysplastic Syndromes are. Before 1982 these were called a lot of different names in the literature like refractory anemia, refractory cytopenias, alloga blastic leukemia kind of suggesting that this could turn into leukemia, but it was the French, American and British classification in 1982 that pulled these all together. People with these disease typically present either asymptomatic, you go in for surgery, you go in for routine blood counts, for a physical exam, your blood counts are low or you present with signs or symptoms of consequences of those blood cells being low. So, red cells are low you're anemic, you might be short of breath with exertion, you might be tired all the time, sometimes you get headaches, you can hear your blood pounding in your ears, things like that. If your white cells are low maybe nothing will happen or maybe you'll get infections. Most typically infections at those sites of your body where the white cells are so important, sinusitis, pneumonia, skin infections that we call cellulitis and if the platelets are low people might have unexplained bleeding or bruising. We now know that these are what we call clonal myeloid stem cell diseases. The bone marrow is constantly reproducing the cells there to make blood throughout your lifetime from a finite group of stem cells, cells that are able to develop into white cells, red cells and platelets and what goes wrong in Myelodysplastic Syndrome is something causes those stem cells not to develop normally. So, there's dysplastic and I'll show you what we mean by dysplastic or abnormal development of those white blood cells, red cells and platelets and we know that there is a finite risk of this disease turning into acute myeloid leukemia over time and that risk depends on a lot of factors that we could talk about.

The way that this diagnosis is still made in 2016 is by looking at the cells under the microscope and this is not an easy diagnosis to make and one of the things that I'm sure Stuart does at his center and we do here and all major academic centers do is before we actually start talking about prognosis and therapies for our patients with Myelodysplastic Syndrome, we review the blood, we review the bone marrow and if we ask you to have another bone marrow biopsy it's not just self-serving because we do it better in Birmingham than they do it Dothan. It's not that. It's that we need to look at those samples on a very well stained slide so the preparation is very important and sometimes we get inadequate samples to the best of the ability of any of us the first one might be inadequate to really make a diagnosis. So, a very good bone marrow sample is important and I'll show you that

Now, in 2008 the World Health Organization kind of changed the classification a bit, but we're not going to get into all of those details, but one the things they did in that classification is they made it quite clear that we're going to consider the Myelodysplastic Syndromes cancers. They weren't considered cancers until recently. There's good and bad to that designation. It doesn't typically develop like lung cancer or breast cancer where it's in one spot and then you could cut it out and just prevent it from spreading. This is a disease that's already throughout the blood and the bone marrow. The reason why we call it a cancer is I'll show you that it's due to genetic changes.

So, the incidence of this disease goes up with advancing age and this is really important. This is not a disease of younger patients and you can see on the bottom axis, the X axis, this only goes down to less than 40 altogether. Very few people out of 100,000 that basically 1 in a million under the age of 40 might develop this disease where if you're over 80 its about 36 out of 100,000 develop it and all of these numbers on the incidence of the disease are probably underestimates because they require a bone marrow biopsy to be done and in older people with other medical problems, their physician may say this really looks like MDS and I'm not going to bother putting someone through a bone marrow biopsy. So, these are probably underestimates.

So, how do we make the diagnosis? Well, first the doctor looks at the blood smear and we'll see funny shapes and things going on with the cells. That's what dysplasia means. The appearance of the cells is abnormal. So, on the left is that normal blood smear I showed you before. On the right you can see a number of things. First of all there's more space between the red blood cells on the right than on the left and that's because the patient is anemic. It came from a person who had a low hemoglobin. You'll also know there's much more variation in the size and the shapes of those red cells. They're not all circles. Some of them are kind of oblong. Some of them are big ovals. Some of them are called tear drops. I think it's right there. It looks like an upside down teardrop there. So, different sizes and shapes we call it anisopoikilocytosis. In the bone marrow we will look for characteristic changes in the appearance of the bone marrow cells. The red cell precursors typically look like this, but sometimes they're giant. This is called a megaloblast. Sometimes they have multiple nuclei in them and if you stain for iron you'll see the iron showing

up as blue distributed around the nucleus of these cells and those are called ring sideroblasts. Those are all signs of dysplasia.

The trouble with any sign of dysplasia that we see, any sign, is that it will not be specific for Myelodysplastic Syndrome. So, it adds to the difficulty in making the diagnosis. So for example, I'm just picking out one of these signs, these ring sideroblasts. At the bottom is MDS, but you could see there's a long list of other things that can cause it. So one of the jobs of the hematologist is to make sure there's not something else going on that might be causing these same appearance in the bone marrow that's not MDS and this is just one example, but I didn't show you is I could have shown you that giant megaloblast on that prior slide, this, and this could be seen in vitamin B12 and folate deficiency. So, it's really important to rule out other causes.

How about the white cells? The white cells typically have the segmented appearance and all these granules, but in myelodysplasia you'll see that the nuclei only have two lobes often and this one has so few granules that you can't even see where the cells begins and ends and the reason why that's important is remember it's the granules that have the enzymes that kill bacteria. So, myelodysplasia may be a double whammy to our ability to fight infection, a low count which is bad and then the cells that are there are not affected.

Now, normally those white cells that you see are made by a very orderly production of these cells. It starts with this cell the most primitive cell that we could recognize in the bone marrow called the blast. A blast is a normal cell in the bone marrow. It's supposed to, however, develop into blood. So for example, in this photomicrograph I took from one of my patients the next thing that happens this cell starts to get some granules in it, those blue dots, and then those blue dots go away and you start to get more salmon colored granules mixed in so it looks a little grayish. The nuclei start to get indented. They're not round like they are here. They start to get indented. Those are called metamyelocytes and then they get so indented that they just look like a... this is called the band where the nucleus is just this linear thing and then it starts to get segmented. This is the normal process that occurs. In Myelodysplastic Syndrome we will see an accumulation of those cells called blasts and that's important prognostically. The more of those there are the closer the person comes to having their disease turn into acute myeloid leukemia and when more than 20 percent of the cells are these it's called acute myeloid leukemia, but these pictures show other changes that we might see. For example, in this photomicrograph here we don't see a lot of neutrophils. It gets to this band form, metamyelocyte form, but it doesn't continue to develop into a segmented neutrophil and that's called shift to immaturity or left shift.

And platelets can look large and dysplastic like here, have very few granules and the cells, the megakaryocytes, instead of having what I showed you on that bone marrow where the nucleus is large and kind of like a popcorn kernel, it just looks unilobate or you could have multiple separate nuclei.

Well, that looks important but that does not belong there. So, I'll come back to it somehow. I hope I copied that somewhere else.

So, here's the World Health Organization classification of MDS and I'm not doing this for anyone to memorize it. That's what we do. What I'm pointing out here is the way that MDS has been classified has been based on the number of these blasts cells in the bone marrow, the number of ring sideroblasts in the bone marrow, the number of cells that have dysplasia. That's what all of these words on this slide mean. In other words, by and large the diagnosis has been... the classification is based on what the pathologist sees under the microscope. There was a hint of the future though in this classification from 2008. Down at the bottom they called out one MDS that's associated with the chromosome change. So, let's get to that because your doctor or if you come for a referral may talk to you about genetic changes that are present in the bone marrow and we can look for these genetic changes in a number of ways. We can look at the chromosomes in the cells and then we can look at single specific genes that can be altered. Now, before I launch on this discussion with my patients in clinic, I always start by saying that the genetic changes we're talking about you weren't born with. They were acquired during your lifetime. Don't know exactly when, but they were acquired and they weren't acquired in every cell in your body. It's only in the bone marrow cells. They mark the disease and we believe that these genetic changes have a lot to do with the disease actually happening. Why do those genetic changes happen? Bad luck, mistakes that are made when these cells are dividing or maybe they're triggered by environmental exposures or ionizing radiation, a number of things. We basically don't know. We do know, however, that the disease occurs with increasing frequency with age and so what we believe is the most common reason why this happens is that from the time we are born to the time we die during that time the bone marrow is constantly replicating the stem cells over and over and over again to create blood and mistakes happen. Now, in the bone marrow cells, in all of our cells that divide, there are mechanisms to prevent these mistakes and kill the cell if the mistake occurs, but sometimes these go awry and so what we think is happening is that there is an acquisition of genetic changes that ultimately lead to the disease and this happens as we age. Well for years the only way we really had of looking at this clinically in our patients is by looking at the chromosomes. What we're looking at here are chromosomes that came out of one cell of the bone marrow and you'll notice here that there are long ones and short ones and they have these dark bands on them produced by the staining. Well, what a cytogeneticist does in the lab is they take this chaos that spilled out of cell in the laboratory and they line it up into what we call a karyotype because, remember, you get one chromosome from mom and one from dad and so you'll see that there are pairs of chromosomes, 22 pairs of chromosomes from long to short and then a pair of sex chromosomes. This would be a man, an X and a Y, as opposed to a woman be two X's and what they look for are mistakes, but what they're looking for are huge mistakes, big pieces of DNA moved around or deleted. That's all they could see because this is under the light microscope. So, this arrow will point out that out of all of these chromosomes that look normal the long arm of chromosome seven is missing and that's what the nomenclature down here means. This one shows you that there are a number of changes. The changes can be numeric like a whole chromosome 22 is missing, a whole

chromosome 20 is missing or there could be things added onto chromosomes like something added to make chromosome 14 longer or parts of chromosome seven can be deleted either the long arm or the short arm and so multiple changes can be seen. Another very common one is loss of genetic material from the long arm of chromosome five. Well, this is important because all of this information has now been included into prognostic systems and there are a number of them out there. The first one that we still use today is called the International Prognostic Scoring System. It's published by International Investigators and Peter Greenberg at Stanford was the lead author here and what they notice is that when they looked at about 800 patients with Myelodysplastic Syndrome that there were certain factors that predicted survival or the disease turning into leukemia. The number of those immature cells in the bone marrow, the chromosome analysis and whether the patient had trivial low blood counts, they're just a little low, but they're not bad or just anemia or if all of their blood counts were low and what we can do is we can get some idea of the natural history of the disease if you do nothing and that's important to understand all of these patients here that were being analyzed just got transfusions. This is not a person's prognosis with transplant or with Azacitidine, for example, and what we could see is patients who have worse chromosomes or more blasts or more cytopenias the high risk patients here have very short survivals and people who don't have those risk factors have longer survivals. Of course, this means though at 10 years even in the better group only 10 percent of people were still alive. If you come out like this and this about 10 percent. So still a devastating disease, but we can prognosticate a little bit better. We also know that those risk factors correlate with the chance of the disease turning into leukemia for lower risk patients, very low risk compared to the higher risk patients where by three years every patient who's still alive had developed acute leukemia.

I'm going to flash through some of these slides.

There have been a lot of iterations of these scoring systems. More patients have been analyzed, more chromosome abnormalities added to more complicated, revised systems to prognosticate. This one, the revised International System still has the chromosome analysis, still has the blast count, but it's not just whether a person has one, two or three low blood counts. It's how bad each of those blood counts are because that is pragmatically important and, again, you can take those variables and put them into prognostic scores and see how you would do without therapy and that's important when we come to how we use this information.

Well, time has marched on during all of this and we've actually gotten really good now at looking at individual genes in a cell in a disease and so now it's possible at relatively low cost and with very short amount of time to actually sequence the DNA of every gene in a cell. So, if we give you bone marrow sample or you give your bone marrow sample and we give it to a laboratory we can ask them to genetically analyze the DNA sequence of all of the genes in there at a relatively low cost and what we have learned from this is that there are recurring genetic changes that occur in these disease that we think are important in production of the disease and clearly important prognosis. So, this was one of the first studies published in *New England*

Journal of Medicine by Rafael Bejar who was at the Dana Farber Cancer Institute at the time and now has moved out to California. They looked at over 400 bone marrow samples and they found eight... out of all the genes, they looked at all the genes, but they found 18 genes that were frequently mutated, changed. Again, not in germ cells. In other words, you didn't get this from mom and dad. It's not in your egg and sperm. You're not going to pass it onto your children. These are genetic changes that are in the bone marrow and what we found was that half of the patients had at least one mutation and even if the chromosome analysis looked normal, which it does in about half of our patients with MDS, half of those we could see genetic changes and there were certain ones that were more or less frequent.

So, what this shows you is just a list of some of these mutations. One of the more common ones is in a gene called P53 that typically make cells very resistant to chemotherapy and TET2 and ASXL1 which I'll come back to at the end. These are important in the structure of chromatin of the DNA and the nuclei and cells turning genes on and off.

So, these genes can fall into different classifications is what I was saying and it's hypothesized that these genetic changes in factors that turn genes on and off or in genes that control growth and differentiation or in genes that, again, help to turn the DNA on or off in terms of cell... the genes that are active and others are very important in the pathogenesis of the disease and we've learned that they're prognostically important. So if you take people with Myelodysplastic Syndrome and if they have one of these five genes mutated that have a worse prognosis, a shorter time till half of the patients have died - you can see it's less than a year compared to if none of those were mutated and it adds to the prognostic clinical prognostic scoring system. So, I mentioned the International Prognostic score and I said there are people who apparently have a lower risk of death and progression to leukemia, but we have found that even in that subset if they have those mutations in the green line they do worse than people who don't have those mutations even though they were both classified as low risk.

So right now, we have learned a lot about the genetics of MDS, but unfortunately all it's been used for so far is prognostication. What happens to people if they don't get any treatment? What I'm going to come to is the future. How are we going to use this information to make inroads into the therapy of MDS?

Let me talk about some clinical challenges, clinical topics as some of you may be interested in. One of them you're going to hear more about from Stuart at lunch is iron chelation therapy. So, I might go more quickly through these slides, but it might provide a background to what he's going to talk about. There is plenty of data in Myelodysplastic Syndrome that getting transfusions is bad. For example, a large study from the Italians where they just looked at their MDS patients and said if you got a transfusion how did you do, what was your survival compared if you didn't and people who were transfusion independent had a longer survival. Well, that doesn't mean it's because you're getting too much iron from the red cells. Maybe you just have a worse disease, but it's a hint that maybe when you get those red cell transfusions

remember it gives you extra iron that your body can't get rid of and the importance of that is iron, too much of it is toxic to the heart, to the liver and a number of other organs. The Italians also looked at just survival based on the number of transfusions. The more transfusions that you get in a four week period, the worse the survival. Again, is that because you have too much iron from all those, those red cells or is it because you have a really bad MDS and just need more transfusion? This doesn't say it's the iron. It turns out though that if you look at a very poor marker of iron overload and it's called the ferritin level, the higher the ferritin level that also correlates with survival. Here you could see people with a lower ferritin level and here are people with a higher ferritin level. That correlated with survival and so fewer people being alive later on. That's what these curves are looking at. Now, one thing to notice though is that that was only true for people who just have MDS causing anemia. If the MDS is causing other low blood counts they did not see any effect of the iron. So, yeah. Iron might be important, but it also depends on the disease itself. I'm glad Stuart is here. I actually do include his work in my talks and Stuart has done an amazing job looking at not only in this case, but a number of situations, number of questions that we have looking at a wealth of data that we can get from registry data and from the Medicare files about outcomes of patients and basically this is a wordy slide. I'm not going to go into it very much here. What it shows here is that in the MDS population there is a higher prevalence. In other words more people with MDS appear to have things like myocardial infarction, heart attacks, heart failure, arrhythmias, diabetes or liver problems and why did I select these out? By the way his paper has lots of other things it looks at, but I selected these out because these were the things that were more likely to be seen in people with MDS and what a clinician would tell you is that these are all things that could be triggered by too much iron. You see the story we're trying to put here? Maybe too much iron is bad for your health in Myelodysplastic Syndrome. That's the story and in fact when the French looked at patients that were getting transfusions and then just said how did they do based on whether the doctor gave them chelating therapy, treatment to get rid of that iron or didn't. Again, you could see shorter survivals. That's what the curve to the left here means compared to this one. Shorter survival if they didn't get chelation therapy. But that's a little problematic isn't it because the doctor might have decided not give them this expensive drug with side effects because the doctor knew that they had other medical problems anyways. These are older patients and they were probably not going to survive their other medical problems. You don't know from looking at data like this. It's called retrospective data, but what they show was in patients with low risk disease the benefit of iron chelation therapy was even more pronounced than it was if they even had slightly higher risk of disease where there was still a benefit, but you could see it doesn't look quite dramatic.

So, there have been studies looking at the impact of iron chelation therapy and I'm just going to highlight one here and this is using an oral drug Deferasirox also known as Exjade and the new formula that Jadenu. Jadenu. So, two oral products for chelation of iron and what they showed in this study of people with MDS that were treated was you could reduce the serum ferritin which is a marker of how much iron is in your body. You can reduce the amount of plasma iron that's available for causing toxicity and, in fact, this is something that's been seen in many studies. People get iron chelation therapy get the iron taken out of them. Every once in a while we see

this otherwise unexplained improvement in their blood counts as if the iron is also suppressing the bone marrow in some way. So, this is one study that said five percent. I could have shown you another study presented in a meeting where it said the same thing. About five percent patients seem to get better if you took some of that iron out. Here's the problem. Almost half had to discontinue and it's often due to toxicity. In fact there are black box warnings or... I'm sorry, there are warnings at least about kidney and liver toxicities with these drugs.

So, how do we put this together? There are pros and cons. I'm not going to go through this list. Here's what I do. This is a recommendation made by a number of people in the literature. We know that red cells are important for our patients with MDS. We know that with red cells you're not able to get rid of that extra iron. So, there's an increased risk of iron overload and we know that transfusion dependence and iron overload both correlate with increased risk of mortality, but we also know that this is a disease of advancing age where people have other medical problems. We also know that they're very heterogeneous spectrum of MDS. There are some people with high risk disease that will have a short survival regardless of how much iron is in them and so what we think is reasonable to do is employ iron chelation treatment for transfusion dependent patients with lower risk MDS and serum ferritins, something that marks that they already have iron overload especially if they don't have a lot of other competing comorbid or medical problems and Stuart will talk more about this.

How about growth factors for treatment of MDS? Why don't we just stimulate that sick bone marrow to make more? Our bodies make blood because there are hormones that stimulate the bone marrow to make red cells, erythropoietin; white cells, GCSF, granulite colony stimulating factor - that's now been commercialized as Neupogen or Neulasta and platelets, thrombopoietin. So, why not just give a lot of erythropoietin? Pharmacologic doses? Well, this is a slide showing a number of studies that showed that you can basically give EPO or Darbepoetin which is a long acting form of EPO, erythropoietin, and somewhere around 50 percent of people will have a response to the EPO and their red cell counts will get better and maybe even become transfusion independent, but we have learned that the people who respond when we asked the question well, who are those 50 percent who get better? They're typically people who aren't making a lot of EPO already in their body. Maybe they have kidney dysfunction. That's where the EPO comes from. They may not have a lot of blasts in their... or they usually don't have a lot of blasts in their bone marrow. Normal is one to two percent or they have lower risk disease. They have only refractory anemia. The chromosomes are normal and the people who do the best are people don't even need red cell transfusions yet. So, we can predict who's going to be more likely to respond or not respond, but there's been a concern that's been raised about the use of erythropoietin actually worsening the survival of patients. That concern comes from studies that have been done in people with cancer, solid tumors. Breast cancer, head and neck cancer, lung cancer where drug companies did these studies where they wanted to give doses of erythropoietin to help people feel better. If we got their hemoglobins a little bit higher would they feel better and several of those studies actually showed that the survival of the people who got the EPO was a little bit worse than if they didn't get it and so the FDA raised a requirement, put a requirement in that we

have to talk to our patients about the risk of early death or dying earlier from it. Now, I think there are a lot of reasons why they saw those events in solid tumor patients, but reassuringly there's a little bit of data in MDS that that's not true for MDS patients. For example, this is a study that was done in a collaboration between the Swedes and the Nordic MDS groups and the Italians in Pavia, Italy and what they did was they got patients who were either transfusion dependent or anemic and in Italy they were just giving them transfusions and in the Nordic groups they were treating them on clinical trials with growth factors like erythropoietin and what they showed was not only wasn't the survival worse in the Scandinavians, actually it was better. Turned out it was better for patients who weren't getting a lot of transfusions to being with, but it wasn't worse and there was no higher risk of getting leukemia. So, the one study's suggesting that by receiving erythropoietin we're not doing our patients a disservice in an effort to increase their hemoglobin and this is a study from the United States that basically showed the same thing. The survival of people who were giving EPO with or without white cell factors and you could see if anything the survival was better out here than in the ones who got than the ones who didn't... just got supportive care, but the important point that this means it wasn't statistically... even that wasn't statistically significant. So, I think it's safe to give EPO and in selected patients it can help bring up the hemoglobin.

There are a number of efforts to try to use drugs like this, things to stimulate platelet production. So, there are commercially available drugs that have been approved for immune destruction of platelets. One of them is an oral drug called Eltrombopag or Promacta and the other one's an injectable you get weekly called Romiplostim or Nplate and these are things that simulate thrombopoietin which is the hormone that stimulates the bone marrow to make platelets. Well, there's a lot of evidence that these drugs can actually improve not only the platelets but the other blood counts and response has been seen in all risk groups. There have been a number of concerns like sometimes these drugs can actually increase the number of those blasts which, remember, is how we define acute leukemia.

This is one study I'll just show you quickly where it was compared to placebo and what this says is yeah, the platelet count went higher when they got Romiplostim than when they got placebo, but in the patients that have really low platelet counts, so the ones we're really worried about bleeding there was no difference in the risk of bleeding. I know this number's a little bit higher than the one with placebo, but this means it wasn't statistically significant and that was true even though the patients with Romiplostim got few number of platelet transfusions. So, the point here is that it's drug that requires you to come in weekly to your doctor's office, is expensive, maybe there's some concern it increases the risk of progression to leukemia and it didn't do what we really want it to do which is prevent bleeding. Yeah, it might make the platelet count get better and we're all happy with higher numbers, but in the long run it didn't prevent the clinically significant complication. This is a slide showing that with further follow up there was no risk of progression to acute leukemia or death and in terms of stimulating white cells, making the white cell count higher no data that that should be given chronically to people with low white counts. In fact, in one study people who got drugs that stimulate the white the cells in the setting of MDS

had a higher chance of dying than if it didn't, but we should be doctors when we treat our patients and if a person's having a really bad infection or recurring infection you could think about during that short period of time giving growth factors to increase the white count. There's also data that when you give growth factors that stimulate white cells they work with Erythropoietin and can make the red count better and there are down sides of giving these drugs like fever and bone pain.

Let's get onto some therapies. So, I'm going to mention a few drugs that we have that are commercially available and here's the problem. We have very few drugs that are commercially available. There are three drugs that actually work in MDS – Lenalidomide and have been... I should say work and have been approved for MDS – Lenalidomide or Revlimid and then we'll talk about Azacitidine and Decitabine. That's it. That's all your doctor has right now. Got to make that better.

Lenalidomide has a number of effects on the bone marrow. I'm not going to go through it for the sake of time. It turns out it works best in people who have Myelodysplastic Syndrome where part of chromosome five, the long arm of chromosome five has been deleted. So, deletion 5Q. Pathologists and hematologists can often recognize this by the appearance of the bone marrow even before we see the chromosome analysis. Alan List who's now at Moffett, deserves a lot of the credit for showing how active this drug is, Revlimid, Lenalidomide, in people with MDS with deletion 5Q and it was based on they had a large study going on and what they notice in this large study is that there were 12 people out of this large study who had MDS with part of chromosome five missing and they noticed that 11 out of those 12 in that initial evaluation having an improvement in their hemoglobin. So, it led to larger studies like this one showing that in a larger study of 148 patients, two-third became red cell transfusion independent and that lasted on average two years, but you could see this is the longest follow up we have there are still people three and four years out who have become red cell transfusion independent with Revlimid if they have MDS with deletion 5Q. It led to a randomized trial that showed the same thing. I'm just going to skip through those, but it doesn't appear to work as well, it does work to some degree when you have MDS without deletion 5Q. So, the response rate there is lower, only about 26 percent of patients became transfusion independent. It doesn't last as long. The average time that people remain red cell transfusion independent was not 2.2 years like it was in Alan List's prior study. It was 41 weeks, less than a year and, again, it lead to a study of Lenalidomide versus sugar pills, placebo, and very similar. About a quarter of people became transfusion independent and that lasted half of the patients remained transfusion independent for about 33 weeks. So, a little bit of activity. We just don't know how to predict which patients are going to benefit. Recently the cooperative groups in the United States that run clinical trial showed that Lenalidomide with Erythropoietin leads to higher responses than Lenalidomide alone. So, if you use Lenalidomide or Revlimid alone or Lenalidomide with EPO, the people who got the EPO had a higher response rate, and again Alan List at Moffett led that study.

I'm only saying this because Ms. Tinsley's here and she's going to go back and report to him. No, Alan's a good man and good friend and deserves a lot of credit for the development of that drug and leading to FDA approval.

Well, how about people with higher risk disease and I'm going to show you later at the end why I separate it like this. The only curative option for Myelodysplastic Syndrome is to replace your bone marrow and that's abbreviated in the literature, in the lay press as bone marrow transplant, but you'll see one of the most common questions I get is, "Well, what's the difference between a bone marrow transplant, a blood and marrow transplant, a hematopoietic stem cell transplant, a peripheral blood stem cell transplant, stem cell transplant?" There is none. It's just where we get those bone marrow stem cells from. Is it from the blood or the bone marrow? It doesn't matter. For your purposes it doesn't matter. There are some slight differences.

Allogeneic means you get that bone marrow from somebody who is not you and is not your identical twin. That's all allogeneic means. You have to get it from someone else. That's the only curative option. So, what's all this talk about? Why don't we just do bone marrow transplants for everyone? Well, first of all the outcomes of bone marrow transplant with Myelodysplastic Syndrome aren't as good as we would like. Now, this is older data, but remember I told you that very few people under the age of 40 actually have Myelodysplastic Syndrome, but if you look at the patients who have the best chance of living without a recurrence of the disease is for pediatric patients and if you look here at people who are all lumped together as over 45 and except for you and you, everyone in this room is... and you... is over 45. I mean, come on. That's not old. And the average age is 70. So, the majority of people don't have great responses outcomes with bone marrow transplant. I'm going to come back to that. So, it raises the question well what should you do? Should we just watch you or should we do a bone marrow transplant? What's your chance of living the longest because after all that's our job as physicians. At least, that's what I think my job is. If I can't cure the disease that's keeping people on this earth to the longest and with the quality of life to enjoy it.

So there was a comparison of how long people lived if they got a bone marrow transplant or if they got nothing – just transfusions, not Azacitidine or other treatments and what they showed this is Corey Cutler work is it was a complicated decision making model that they did, but what they showed was if you looked at life expectancy in people who had higher risk disease, intermediate 2 and high risk disease, their predicted life expectancy in years was higher if you got a transplant as soon as possible compared to any time after that. So, just looking at all the data your chance of being alive was greater if you got a transplant immediately.

On the other hand if you had lower risk disease actually your chance of being alive... your life expectancy was actually shorter if you got an immediate transplant as opposed to waiting. Okay, that's what he showed. There's a problem with analysis. So another way of looking at it is shown here, okay? And this comes from Corey Cutler. This is how he interprets his data. This is the chance, this is your survival with stem cell transplant. Early on there's a risk of the transplant

graft versus host disease, infections, organ toxicity and so there's a price to pay for going through it early on. There is a risk and I'm talking very bluntly because these are difficult decisions that face our patients, face you, but that's what it is. You're taking an upfront chance for the chance of being cured. That's what this means when this line starts to flatten out that you're going to chance of being alive in the future is stable compared to if you don't get a stem cell transplant. So for low risk patients, the risk of transplant we said was greater than the risk of disease and for high risk patients, the risk of the disease was greater than the risk of transplant, but many patients aren't eligible for transplant for a variety of reasons and keep in mind on top of all of that I was going to say something else... the reason why it's a difficult decision, but I'll come back it later when I do my slides. Oh, actually it's on this slide. Very wordy slide, it says, and this analysis is suggestive of what to do, but it's not really that helpful because when a patient is diagnosed with MDS we often do try therapies like Lenalidomide and Azacitidine and Decitabine. We have options and that wasn't considered in those analyses, so now you have to wonder how do you make this decision today with the treatments that we have and by the way we've gotten better at doing bone marrow transplants, too. So, it's kind of a moving target as to what really is the best decision. Well the only way to do this is to get together our patients and clinicians and investigators and do the study and, in fact, Medicare has required this because Medicare is not going to cover transplants for MDS in the future unless we agree, clinicians, clinical investigators, agree to do this study and basically what this study is for people with higher risk disease, is it better to get Azacitidine or Decitabine or is it better to get a transplant? That's the study. I'm not going to go through the details and so that's what we're doing right now and we have to do this study because at some point in the future, CMS, Centers for Medicare and Medicaid, are going to say we're not covering this for the Medicare population until you show that this expensive procedure is actually a benefit in terms of survival.

Okay. Well, what are Azacitidine and Decitabine? These are drugs that are felt to work by reactivating genes that have been silenced that are necessary for normal blood formation. When that blast cell that I showed you way at the beginning, you're wondering why I showed it, when that blast cell turns into a red cell or a white cell, it has to turn on genes to make all of the proteins for that cell to do it's job and if it can't then the cell is not going to develop normally and we have learned that one of the mechanisms by which these genes are silenced is that the DNA gets methyl groups attached to it. That's what these red lollipops are, and those things silence genes and keep the genes from making the proteins that are necessary for normal blood formation. DNA methyltransferase puts the methyl groups on the DNA. If you treat the cells with demethylating agents and that's things like Azacitidine and Decitabine, over time the methyl groups go away and that allows new transcription factors to go in there, bind to the DNA and turn the genes on again and reactivate the production of proteins that are necessary for normal development, and no I did not do this animation. I would not even know how to do this animation. I can't remember who gave me this slide, but I am going to keep it. I like it.

Okay. Well, there are a couple of hypomethylating agents. One is Azacitidine known as Vidaza and the other one is Decitabine known as Dacogen. We know that in patients with higher risk

disease based on the number of studies that go by names like CALGB and well this is MD Anderson Cancer Center, the ADOPT trial. A number of studies that people who received Azacitidine and Decitabine can have responses and again if you just, a lot of data here, but at best only about 40 to 50 percent of people have an improvement in their blood counts or response. We've been trying to do better by adding other drugs in and this is a study that has been led by a cooperative group that we belong to called The Southwest Oncology Group in collaboration with my colleagues in other cooperative groups that are funded by the NCI like Alliance and ECOG and even investigators in Canada, the NCI of Canada, and we did this large study to see if the addition of other drugs to Azacitidine can make things better, so we compared patients with higher risk disease getting Azacitidine or Azacitidine with Revlimid or Azacitidine with Vorinostat, which is called a histone deacetylase inhibitor based on smaller studies showing that they might be better. Bottom line, unfortunately, they weren't. We tried, but adding another drug, at least these two drugs, didn't make things better.

We know, however, that Azacitidine improves the survival of patients. We know if from a study where patients were put on, with MDS that had intermediate 2 or higher risk, so higher risk disease based on those chromosomes and blast counts that I talked about earlier, and had higher grade disease, this means more blasts, were randomly assigned to either get Azacitidine or just transfusions and antibiotics, low dose ara-c, that's an outpatient thing, or treat is like acute leukemia with very intensive chemo, and people would stay on the Azacitidine as long as they weren't progressing and as long as they weren't having toxicity, and what was shown in the study is that it took 15, well how to say this, 15 months, at 15 months in people were getting those convention care regimens, not Azacitidine, half of the subjects or patients on the study had died, and it was 24 months it took for half of those patients to die. The other way of looking at it is, and I think this is an easier way to look at it when I explain it to my patients, because my patients usually say, "My granddaughter's graduating from college," or high school or whatever, "in a year or two years. What's my chance of being alive then?" They don't want to know if they were in a room with 100 people, what's their chance of still being alive at a certain point. They want to know, you want to know what your chance is, and you can see that we pretty much double the chance of being alive at two years by giving Azacitidine, that's the good news. The bad news is the trajectory of these curves isn't very good, right? We're not curing the disease with these drugs. I'm going to skip this for the sake of time. This wordy slide said it worked in all subsets of patients and, again, it was only half of the patients who had any time of hematologic improvement with the Azacitidine and 45 percent of them became transfusion independent. Very similar numbers across the board. Basically half of the people responded.

This wordy slide I'll just say what it says, that genetic information I talked to you about that we've been using for prognostication, it turns out that it may also predict which people are going to have a better change of responding, so people who have a TET2 mutation had a higher chance of response with Azacitidine compared to if they didn't. So, you can see it's 82 percent versus 45 percent. So we might be better able to select treatments for patients. Unfortunately, when Azacitidine doesn't work or Decitabine doesn't work or stops working, the average survival of

patients is less than a year and you can see very few people are alive two or three years later, around 5 to 10 percent. What's interesting in this analysis and I'm putting this at the end for a reason, is that when they looked at what were the outcomes of people if they got a bone marrow, I think that's the next slide, if they got a bone marrow transplant, it was the best, but actually the survival of people who got anything investigational appeared to be better. It's similar to this, the allogeneic transplant although allogeneic transplant to me looks better to me, the statisticians said they were the same, but in any case both of these were better than any other treatment option, getting intensive chemo, getting another low dose chemotherapy, getting just best supportive care.

So what are the options coming to the end of this talk? There are a number that have been in development and unfortunately a number of these, some of these on this list have basically failed. Again, for the sake of time, I'll just show you a long list of other drugs that inhibit what are called histone deacetylases, which work in concert with things like Azacitidine and Decitabine, very low response rates. There was a lot of hype and hope for this drug, Rigosertib, that is an inhibitor of an enzyme that's important in cells dividing and so it looked promising. So, the company, the drug company, did a large study where people got Rigosertib at the time it was given this letter and number name, versus best supportive care, hoping that by getting this drug after Vidaza or Dacogen had failed to lead to a response, that it would be helpful. Numerically the average survival, the median survival, was a little bit longer with Rigosertib than with best supportive care, but it was not statistically significant. It could have happened by chance this way.

Okay. So, last two slides, where are we? There are investigational agents being developed but right now our paradigm for treatment MDS is... remains pretty simple, too simple, but this is the way it is. For lower risk patients, our goal has become more to improve marrow function, decrease transfusion requirements and the reason for that is we don't have a pill with no side effects that makes this go away, because if we did, of course, our goal would be cure, right? I mean people with lower risk disease still have an outcome that's not as good as people who don't have Myelodysplastic Syndrome. But we don't have that, so right now we focus on improving marrow function and so if therapy is actually needed, we wonder about a roll for growth factors first, anemia, low white count, low platelet count, recurring infections, things like that and if not, if not eligible for just growth factors, if they have a deletion of chromosome 5Q we use Revlimid or Lenalidomide. If they don't, you could use any of those, but these are the only two drugs that are FDA approved for this indication, Azacitidine and Decitabine. Lenalidomide is only approved here so your doctor may have trouble getting this drug for people who don't have deletion 5Q and because remember the responses were lower and they didn't last as long. If you have higher risk disease, we really don't know if the best option is to move directly to an allogeneic transplant or first give a hypomethylating agent and then move to a transplant if this stops working. We don't know.

So, where does this leave us? And by the way, well I'll get to that. So, where does this leave us? We have to do better, obviously, for all of us we have to do better. Now, there's... what I didn't put on this slide, our whole group approaches that are looking at modulating and infecting the immune system because it is clear that the immune system, especially early on, is important in the development of Myelodysplastic Syndrome and, again, I'm not doing this because Nurse Tinsley's here, it's because Allen West has really been a pioneer in looking at the effect of what's called the innate immune system in Myelodysplastic Syndrome and, in fact, a number of drugs that we use and approaches that we use in MDS that I didn't have time to cover, work on the immune system, like immunosuppressive drugs, but we didn't have time for that.

So I think in the near future, how are we going to do better? Well we need improvements in stem cell transplant. We're doing this by increasing the donor options, but we also have to ameliorate graft versus host disease, we have to enhance the immunologic effect of that graft against the disease and we have to make this tolerable if it's going to really be an effective therapy for all, it's going to have to be tolerable for older patients and that is really a long way away at this point.

I think from my point of view, I am not a bone marrow transplant specialist, from my point of view we need to have a more precision approach to therapy. Right now our approach to therapy is pretty inane. Right? Low-risk, high-risk, do you have deletion 5Q or not. I mean you don't have to have a Ph.D. in Biology to be able to remember that.

We have to do better. What we have to understand is what I started with, this is a very heterogeneous disease. It is driven by a number of genetic changes, and so one person's MDS may be very different and how it starts and how it progresses from the next person's. So, we have to do a better job of collecting data on every one of our patients of the genetic changes that are occurring and then targeting those genetic changes that are driving the disease. This isn't pie in the sky. What I haven't had time to talk about is the development of drugs in acute myeloid leukemia, not yet MDS, but a sister to this disease, that do target some of the genetic changes like IDH1 and IDH2. Others will be coming. And as I mentioned, I think that we have to look at the role of the innate immune system and inflammation and target that as well. These might be on two of the areas that are most ripe for development, so not only in terms of our future we must do better, I think we will do better, but we'll have to do this as a concerted effort between clinical investigators, funding sources and people living with Myelodysplastic Syndrome, because without you we can't develop new therapies that are so sorely needed in these diseases.

So, thanks for coming this morning. I appreciate the invitation to speak and I'd be glad to take any questions.

Q1: Did I miss the Aranesp and Procrit in your discussion, which is what I'm on now?

Harry Erba, MD, PhD: Yes. I'm sorry I didn't hear.

Q1: The question is I'm on Aranesp shots every two weeks. They try to keep it at the levels that they are now, did I miss it in your presentation?

Harry Erba, MD, PhD: I missed the last part.

Q1: In the presentation?

Harry Erba, MD, PhD: Yeah, that's because I talk too much. I know that that is the problem. It's not you, it is me. There's so much to talk about. OK, so this looks at, a metaanalysis, there've been hundreds and hundreds of studies of EPO, erythropoietin, in it's various forms. Just erythropoietin, different brand names like Procrit and...

Q1: Aranesp?

No, not Aranesp. Procrit and what? Epogen. Thanks! I was just blanking. Procrit, Epogen, brand names of erythropoietin and then there are long-acting forms of the same molecule and that's Darbepoetin or Aranesp. So, we know that what a meta-analysis is, is taking all of these studies that are done differently and different places, you know, little nuances and basically saying, what can we expect from this, from these drugs? And what we're seeing here is that when they look at people getting Darbepoetin, so you're getting Aranesp every two weeks. This was, and people getting this dose per week, 50 percent had an erythroid response. The hemoglobin went up and/or they became transfusion independent. When they got a higher dose in these studies it looked like it was a better response, so this was every week. If GCFS was added, it didn't seem to make any difference compared to here. In fact, it looked a little bit lower, and when it was given every two weeks, it seemed the same as giving this dose every week, but a higher dose every week seemed to be better. So this author, I'm quoting with Valeria Santini said, the opinion of this author was that if you give it every week at a higher dose you might get a higher response rate. I'm not sure we can say that. I think what we can safely say, I kind of generalize things, what I say is about half of the patients respond. This is looking at IPO, at a standard dose, at a higher dose or with growth factor and, again, if you look at these studies, it's about half of the patients are having an erythroid response and some of these people have become transfusion independent. That's what the green lines are. What's really much more important though than just taking a meta-analysis, which is just take, meta-analysis takes everybody, all these studies, all the patients. We know that we're getting pretty good at predicting who's going to be in this group and who's going to be I'll say in this group, the remainder who don't respond and what we've learned is that if we measure before we even start the Aranesp or Procrit, how much erythropoietin your body's making and it's a less than a certain number, that's good. If it's really high, it's really, really unlikely to benefit you. And if you're transfusion independent, so for example I'll quote one study. In one study where this level was less than 200 and a person had not yet received transfusions, the chance of responding would be 75 to 80 percent. Very high. If you were getting lots of transfusion or your level was 500, your chance of responding was 5

percent. So, I could say you have a 50 percent chance of responding based on everyone, but you're not everyone. You're going to have certain characteristics and I could get a little bit more specific. Before I let you get to your point and there are other things about the disease that we know have been helpful. So, for patients who have higher risk disease or more blasts in the bone marrow, it doesn't help. So, I usually don't use it.

Q1: I'm eight months into it and the shot every two weeks alternate between 8.6 and 9.2. So, I get it, I was checked it's 9.2 and my hemoglobin, but by the two weeks it's down to 8.6, but only 8 months into this I've been hospitalized once and I've had three transfusions already. So, I just recently got off .7 or 7.2 hemoglobin where I had to get two units of blood. So, I'm kind of brittle.

Harry Erba, MD, PhD: Okay. So, like I do it, when I use a drug in any of my patients with any cancer, you pick a drug and the benefit that we want to see with that drug is that you become transfusion independent. That's the hope. At least that and that hasn't happened yet. So, what I would do based on some of this data that is here, I would go up on the dose and so usually, I'd be interested in hearing what Stuart does, I might wait two or three months to see what's happening and if you, because it takes a while to figure out if you're responding and if you haven't responded in the first two to three months, I'll go up on the dose, either you can see if you can do it weekly or go up on the dose every two weeks and then other thing that you can do in that situation is that there's some data that when you add growth factors that stimulate the white cells, it actually helps the red cell count get better too and specifically, again, we've learned by looking at which patients might that help. For some reason it seems in several studies that people who have the MDS with ring sideroblast, those are the ones who seem to benefit the most by adding in the GCSF.

Q1: Thank you. And I do have some other, the cause of mine has been diagnosed here and confirmed pretty much (inaudible 1:13:06) AB, I got a second opinion, that I'll have RA. I have rheumatoid arthritis and I've been taking some Enbrel and everything for 15 or 16 years. So, it started up here in Kirkland Clinic and they seem to think, both places is that's what caused the thing and I do have three mutations and I do have to take a transfusion once a month for my RA, so I don't retest it. So, I don't know if that's affecting, there's a little more complication than maybe the MDS. So, we'll get into that I'm sure.

Harry Erba, MD, PhD: Yeah, there are other medical issues can complicate, so rheumatoid arthritis causes inflammation can also lead to anemia. I'm not disagreeing at all and I don't know your case, but the point you bring up is an important one. When I'm thinking about that, well it used to be a pad of paper, now it's the iPad or the iPhone with the questions and somewhere at the top of the list is why did I get this? And, the bottom line is we will never know for certain in the individual person. What we can say is that when you look at people that in your case, have been treated with drugs like Enbrel there is a higher risk of getting other malignancies especially lymphoid malignancies, but also now MDS has been associated with immunosuppressive

therapy. In your body, do I know that the Enbrel triggered something that led to the MDS exactly in you or is it that you have RA and getting Enbrel and something else did it? I don't. It's a moot point anyway because at this point it doesn't affect how we prognosticate or treat.

Q1: Thank you.

Harry Erba, MD, PhD: I took too long, so I better let you get on.

Q2: Could I ask a question please?

Harry Erba, MD, PhD: Oh yeah.

Q2: Okay. So, we're at the point where we're still struggling with the... we're still having to have quite often, transfusions and we're dealing with iron overload. Did I understand you to say that the erythropoietin was a other option if we are continuing to have to have these transfusions?

Harry Erba, MD, PhD: It depends on the situation, but it could be, yes. Again, it depends on whether I choose to use EPO or not, erythropoietin, depends on some of these things. So, I'll have a discussion with patients. So, I'll know if they... so if you have a lower-risk disease and that's by looking at the chromosomes and the blast count and you're anemic, then I will look at the endogenous erythropoietin level. If it's 1,000, I'm really, really, really unlikely to say you should try this. Is it wrong? I don't know, it might be wrong, but you could try it, but it's usually a waste of time. If your body is already responding by making a lot of erythropoietin, giving you more erythropoietin is likely not going to be the answer. So, that's part of it. If the blast count is elevated, for example, if there are chromosome changes, so I look at all these factors and I say, you know, "Gee, you really have a great chance at responding to EPO, we should really try it," or, "You know, I don't think it's going to work." What I do in that situation though, if there aren't a lot of options and this is important and I don't think it's done enough in general in the MDS community is whether you think you have a great chance of responding or a low chance, it's not a drug that you should be committed to for life if it's not working. I mean, you look at and this is why I got to your point that you're still transfusion dependent, my goal is to get you transfusion independent and typically if you don't see responses in three to six months, you're not going to. People quibble about whether it's three months or six months. With all of these drugs, Revlimid, Azacitidine, it could take a while, but you shouldn't be on it for two years and still getting transfusions. So, sometimes I hear, "Yeah, but imagine how many transfusions I would get if I wasn't getting EPO." That might be true, but I don't have to imagine. You could stop the EPO and see if it actually makes a difference. So, I don't think we do enough of that. The point I'm getting to is that there's nothing wrong with a trial of erythropoietin. We can predict how likely that trial is to work based on some of these factors that we've learned, but there's nothing wrong with a trial as long as we understand it is a trial and if it doesn't work then there's no reason to continue it. The other thing I'm just going to say about the dosing of EPO that drives me personally crazy is that you can't actually give erythropoietin to get your



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hemoglobin normal and I think part of it is because of the concerns from those solid tumor studies where people died or had a higher chance of dying than if they didn't get it, and so our regulations are if your hemoglobin is above 10 you can't get it at that point. We're not there for you yet.

Q3: I check it every (inaudible 1:18:30).

Harry Erba, MD, PhD: There's no reason to not try a higher dose or, I think, you said two weeks, and ...

Q3: (inaudible 1:18:46)

Harry Erba, MD, PhD: OK, thanks.

(Applause)