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Melhem Solh, MD: … a little bit about Myelodysplastic Syndrome. Thank you for showing up. I am Dr. Solh from the Blood and Marrow Transplant at Northside Hospital. I'm going to make this informal. Feel free to interrupt, ask questions if it applies to you, to a friend, and so on. Sometimes it might be a little bit too much, just say hey, back off. What do you mean? I'll be more than happy to explain. Okay?

So, who had a bone marrow biopsy here? Raise your hand. Alright. Fair enough. Now, was that pleasant or painful? How did it go? Not fun? Well, the reason we put your through the bone marrow biopsy because inside your bones is a tiny space that's a factory where all your blood is being made. This blood cells starts from very immature blood cells. We call them the blood stem cells. Your blood stem cell makes three different kinds of blood. It makes your white blood cells to help you fight infections, it makes your red cells to carry oxygen around to your organs to keep you alive and it makes your platelets that will keep you from bleeding if you fall down or if you cut your finger. So each one of these cells, we call them the mature blood types, the white, red and platelets, they go through different stages of maturation. They start at the stem cell at this level and they go through different levels of maturation then they become a fully mature cell that has a function. So if you want to think about it like us, we start as infants. We become toddlers, teenagers, till you become a grownup who has a job who has a function in life. Same thing with our blood cells. What Myelodysplastic Syndrome is you're getting stuck in the middle? These cells are not making it all the way to a functional level where they have a purpose of their blood function. I usually call them the teenager cells because they are in the middle they don't know what the heck they're doing, they're confused and they cause trouble. So, that's what your Myelodysplastic Syndrome. Problem if you leave a teenager as a teenager forever they're going to get in really bad trouble which is what we call the acute leukemia because these cells can become more and more immature with time if we do nothing about it and develop a blood cancer that will cause the acute leukemia. When that step happens, it's very serious. We try to treat it very aggressively and we talk about few options if we reach that level.

So, what Myelodysplastic Syndrome most of people believe it's a disease you're going to acquire as you get older. However, I've seen people in their teens and their 20s who come up with Myelodysplastic Syndrome, but in general it's older age group disease. As you see in folks above age 80 the incidence is about 10 times what you see in people in their 50 to 60. So as we age, it's we're all prone to develop this disease. There are so many risk factors that can happen, but almost 99 percent of patients I see they haven't been exposed to anything in their lifetime

that makes them develop the Myelodysplastic Syndrome. Some of the things that can lead to Myelodysplastic Syndrome if you've had chemotherapy before. People who had breast cancer or lung cancer have been treated with chemotherapy are prone to develop this disease three to five years later. If you had radiation before, you're prone to develop this. Work in a nuclear testing and chemical factories you are prone to develop some blood disorders including Myelodysplastic Syndrome. Some believe that if you've been to Vietnam during that war you got exposed to Agent Orange. Many people came back with a disease called multiple myeloma and some risks of Myelodysplastic Syndrome, but as I said almost 9 out of 10 people I meet in the clinic who come for Myelodysplastic Syndromes they haven't had any of these exposures.

The way we diagnose Myelodysplastic Syndrome is you present to the clinic with most of the time it's a blood test that… a routine blood test. You have anemia or you have a low platelet count or a low white cell count or sometimes you can present with an infection or a bleeding as a result of this low counts. So first thing your oncologist going to do is rule out other reasons why you have this low count. Be sure you're not vitamin deficient, be sure you're not taking medications causing these problems, make sure you don't have other benign blood problems. The next step is to do the bone marrow biopsy where we look at that teenager cells that I told you about. You're going to look at those cells. We'll call them dysplastic cells. It means they are not maturing enough. They're looking abnormal, but they are not a full blown cancer cell yet. With Myelodysplastic Syndrome you can still see some blood cancer cells in the bone marrow. So back in the days, a group of experts sat together and put a cutoff limit of what we call the 20 percent blast cells above and below. So if we do your bone marrow biopsy and we see less than 20 percent cancer cells, we call it Myelodysplastic Syndrome. If we do your bone marrow biopsy and we see more than 20 percent of your bone marrow as cancer cells, that's when we'll call it an acute leukemia and this a transition I was telling you about that if you have somebody with Myelodysplastic Syndrome that's slightly higher risk, you do nothing about it. They're going to all develop acute leukemia eventually at one point in their life.

Any questions so far?

So, how do we classify MDS? So, you walk into the clinic. We figure it out you have anemia or low platelet count. We did the biopsy. The pathologist calls us back, "Yes, Mr. So and So have Myelodysplastic Syndrome." The first thing we try to decide is how… what's the risk status of this disease. Myelodysplastic Syndrome people can live anywhere from few months to 15 years depending on how good or high is your risk of the Myelodysplastic Syndrome and we base this on multiple factors. So as you can see over the years, we've come a long way how we look at this disease. Back in the days the way we looked at your risk status was we put the slide under the microscope, we look at the cells and the pathologist will say, oh, these are looking bad cells. They're of this type, so and so, and we're like oh, this is a bad disease. As we've gotten better at this we started understanding actually it's not just how the cell look, it is what your blood counts, it's how many cancer cells you have in your bone marrow, it is what kind of chromosomes you have acquired as a result of this disease in your cells that's putting all together to give you a risk

score. The most common two risk scores we use nowadays are called the IPSS and the revised IPSS. So, IPSS stands for the International Prognostic Scoring System.

So, we look at three things when you come in. The IPSS which is the older risk score. We look at how much cancer cells you have in your bone marrow. We look at your chromosomes. So, we send your cancer cells for chromosomal testing to see is there any abnormal changes on these cells in terms of their chromosomes and we look at how many cytopenias do you have. Do you only have anemia? Do you have anemia and the low platelet count or do you have low white count, low platelet count and low blood count and we'll give you a score for each one of those based on the numbers that we find on your bone marrow, on your chromosomes and on your blood. At the end of the day, we'll give you the total score. So as you can see with the total score, you can range anywhere from a low risk disease to a high risk disease. Somebody with a low risk disease can live six – seven years and even more than that. Someone with a high risk disease their survival is only .4 year which is six months. So, this is a disease where the range of how well you're going to do is going to highly depend on what's going on with all these factors. The problem with this score the reason we changed it a couple years ago, it just… so somebody who has a anemia with a hemoglobin of 10 is going to be counted just the same score like somebody who has anemia of a hemoglobin of five and we always knew as physicians these are not the same patients. The one who has a very low hemoglobin is definitely a higher risk disease. So, the new scores that came was called the Revised IPSS. So if I see you in my clinic that's what we're going to go by is the new revised IPSS which was an update from the one I just show you. What this takes into account it still looks at the karyotype or the cytogenetics, the chromosomes, still looks at the cancer cell count, but when it comes to cytopenias it gives you a different scores based on how deep your cytopenia like how low is your hemoglobin, how low are your platelets and your neutrophil count. So, somebody with a platelet count of 20 is going to get the higher score than someone with the platelet count of 75. The older scores are used to get the same number.

So, this was in 2012 this one this score used and we've been validated it with several big cohorts of studies comparing to the older score. So, many centers now especially transplant centers, this is what we go by to decide if you're somebody who's high risk enough who's going to need transplant or not. So at the end of the day you get a total based on your, as I said, the same factors, chromosomes, cancer cells and the depth of your cytopenias.

Any questions so far?

So… go ahead.

Q1: … my understanding of cancer cells, they continue to grow out of control. It starts off low. Does that same process happen in cancer cells in MDS?

Melhem Solh, MD: So with MDS when we put that risk status, it tells us two things. It tells us what your survival going to be and it tells us what are the odds of you becoming an acute leukemia in the next one to two years it's going to be. So, the risk you are the more likely you're going to develop into a full blown acute leukemia and most people with MDS who are going to die is the high risk group is because they developed the acute leukemia. So, yeah. If you have 15 percent cancer cells they're going to go above 20 and it was in a year at most. If you have one to two percent, it's going to take much longer than that to get to the 20 percent and that highlight depends on what kinds of chromosomes you have on those one to two percent. If you have the high risk chromosomal abnormalities you're going to reach the 20 much faster than somebody who has normal chromosomes or a good risk chromosomes.

So first thing, we did the diagnosis. Number two we decided risk group you fall into. The third step would be how are we going to treat this Myelodysplastic Syndrome? So in general when we look at Myelodysplastic Syndrome, we look at the low risk group, we'll call them low to Intermediate 1 risk and we'll look at the higher risk group. These are treated slightly different because as I showed you somebody in the low risk group can live six to seven years. We have time to get aggressive with them. We don't have to be too aggressive from day one. Someone in the high risk group who has a projected survival of one year or less, we have to be aggressive from day one otherwise we're not going to make it. So for low risk who most common problem usually is anemias that we have to deal with. We have to get transfusions and so on. The way we treat this is 1) we look at the chromosomes, as I said. So, there is a chromosome that people can develop called deletion 5. So, that's chromosome number five on your cells that can be deleted. This is a very unique chromosomal abnormality in Myelodysplastic Syndrome because people who have this problem is considered a good risk. Even among the low risk patients they have a good risk disease and they're a good risk only because of this drug. It's called Lenalidomide which works great in this group. So, always check with your doctor that you have this deletion 5 or not. People who have deletion 5 who gets this drug, they have survival more than 9 – 10 years. They can go on long remission and this is given as an oral pill. So, it's very responsive in this subset of patients. So if you have anemia and you do not have the deletion 5, ideally if you're still a low risk the first step we do is try to push your bone marrow to make more blood. So, we'll give you things. We'll call them the growth factors. Have any of you had Aranesp or EPO? So if you're a low risk group, you have low hemoglobin that's what you're going to start with. These are benign drugs. They'll try to push your bone marrow to make blood. Problem with EPO and Aranesp they're going to only work if your EPO level is low. So if you're not making that growth factor by your own, by giving it to you it's going to help you, but if you have a high level of it already in your blood, it's not going to work. So before I recommend EPO or Aranesp to anyone, I usually check their EPO level in their blood. Is it low? Is it high? That will give me an idea are they going to respond to it or not. People who don't respond to EPO or Aranesp, an option for them is to consider this drug even if they don't have the deletion 5 and we'll show you some of those results as well.

Q2: Is that the same as Revlimid?

Melhem Solh, MD: Yes, it is Revlimid. So, the drugs that are most commonly used for MDS is Lenalidomide which is Revlimid and the group of drugs we'll call them the hypomethylating agents, Azacitidine or Vidaza, if anyone has taken it here. I know of somebody for sure. Decitabine which is Dacogen. So, they are pretty much the cousins. They are the same group of drugs. They work the same way and it's your physician's choice what they usually give in their office. There is no preference over one or the other.

Q3: Procrit (inaudible 15:05)

Melhem Solh, MD: Procrit is this one here in the low risk is the EPO. So, the other name for it is Procrit. The long acting type of it is called Aranesp. So if you have a low risk disease that's where you're going to start with the Procrit. If you don't respond to the Procrit, you're going to move to one of these drugs.

Q4: What about the Aranesp?

Melhem Solh, MD: That falls in the same group with those the growth factors. So, we call them Erythropoietin stimulating agents. So, Procrit is a short acting. The Aranesp is a long acting drug. So, they work the same way. So if you're taking one or the other, you're going to get the same results. Aranesp is you get it every few months versus Procrit you have to get it more often.

Q5: (inaudible 15:52 – 15:55)

Melhem Solh, MD: So if the EPO is less than 500, they are more likely to respond to Procrit or Aranesp because you're not making that hormone in your blood. So, by giving it to you you're more likely to respond. If you have a high level of it in your blood by giving you more of it is may work, but the odds are much less.

Q6: Which is Vidaza?

Melhem Solh, MD: That's the Azacitidine. So, this is a Vidaza and Decitabine is a Dacogen.

So when do we use Revlimid in MDS? The FDA has approved this drug to be used in patients as I showed you before who have a low or Intermediate 1 risk MDS who has deletion 5Q with or without other chromosome abnormalities. So if you're on the lower risk you have that deletion 5Q, this is a great drug and pretty much it's a standard of care. Wherever you're going to go you have that chromosomal abnormality, you have a low risk disease, you're going to get this drug and this is based on actually multiple studies. I'm just going to show you a few slides. So when we talk about other drugs and other groups you know the difference why this is such a breakthrough in treatment of MDS. So, what they did in this group they took people who have MDS, low risk, who are transfusion dependent. So, you're getting at least two units of blood

almost every month and they put them on Revlimid 10 milligram every day versus Revlimid for 21 days and we followed those patients to see are there requirement for blood transfusion going to go down or are they going to become transfusion independent all together. What we found is actually about three-quarters of them 67 percent, two-thirds will become transfusion independent. So, you jump from someone who's getting two to four units of blood a month to requiring zero units in about 70 percent of the cases. Three-quarters will have either become independent of blood transfusion or it will go down by 50 percent. When we look at the chromosomal abnormalities that they had on their cancer cells or their dysplastic cells, almost half of these patients that deletion 5, that chromosomal abnormality, disappear. So, this is one group of patients. If you're… Well, you're never lucky by having MDS, but if you want to pick one MDS subtype is the one with deletion because you're going to do the best long term.

Q7: What if you do not show del 5?

Melhem Solh, MD: Very good question. You still have a response, not as impressive as this one as a del 5 and I'll show you some of those results. So someone who's not a high risk who's having anemia and requiring transfusions, it's still an option even if you don't have the del 5. You'll have a response rate about 30 to 40 percent. The thing about it it's a pill. So, you don't have to come back and forth to the clinic five to seven days a month to get injections. So, it's something we still try it without the del 5, but if someone has a del 5 that doesn't get that drug that's a big no-no.

Q8: Which one (inaudible 19:18 – 19:24) but they still didn't (inaudible 19:27 – 19:30).

Melhem Solh, MD: So, you'll get Dacogen, you'll the Revlimid. Have you spoken to a transplant doc yet?

Q8: Not yet.

Melhem Solh, MD: Alright. So, pick a card at the end of this session and come see us because you're in that group.

Q8: That's why she's here.

Melhem Solh, MD: Because once you fail, I'll show you the results. It's pretty bad if you don't get the transplant.

Q8: So, (inaudible 19:54).

Melhem Solh, MD: That's a good risk. So by itself, it's a good risk.

Q8: (inaudible 19:59).

Melhem Solh, MD: Yeah. So and people who have del 5Q the responded irrespective of their age, gender, what their score was a low or intermediate risk score or the cytogenetic pattern. The only group that didn't fare as well if you had a very low platelet count or if you were needing more than four units of blood each month, but still had a very good response, but not as good as the rest of the patients who got this drug.

So for those of you who have been on Revlimid there is some side effects for it. The most common side effect, don't bother about this, is your blood count is going to drop down in the beginning. So each time you treat MDS or leukemia the blood counts are going to go down before they get better. So, if you start those medications and you see your hemoglobin got worse first month or two or your platelet count got worse, don't panic. It doesn't mean you're getting worse. It just means the drug is doing what it's supposed to do. It's killing the bad cells, so it leaves room for the good ones to come up. So technically, you're going to see a drop on your counts. It's going to recover after two to three cycles and your doctor will adjust the dose, so your blood counts stay at a certain safe level.

So, coming to your question if you do not have the del 5Q what happens? You should have been on a clinical trial network actually. This question has been going on for several years. So, they looked at people who don't have the…

Q8: You won't get this one good.

Melhem Solh, MD: The del 5Q and we did the same thing to them. We give them the Revlimid versus the three weeks and you can see the response. I showed you on that slide was 76 percent. So, you still get that response in 43 percent. So almost half the patients will have some response to Revlimid if you do not have the del 5Q. Not as impressive as the group that has the isolated 5Q but still an option and for people who responded their hemoglobin increased by 3.2 grams. So if you're someone whose hemoglobin is six, seven on a regular basis needing transfusion if you respond this drug you're going to see it go nine or 10 where you're not going to require transfusion anymore and the time for response. So, if you get any… this is we're talking about the non-5Q group. If you get a response to the medications, the duration of that response is about 10 to 11 months. So, you'll get a year out of this drug before you have to move to the more aggressive medications like the Vidaza or the Dacogen if you do get a response. The trick about it is you have to be patient because it takes about three rounds to start seeing a response. So if you start it today on average you're not going to see a response till October. It takes about two to three months to see that response. Some people get tired of it too often because in the first month or two you're going to need more transfusions than what you're used to, but be patient to see if the drug is going to work or not especially one as I showed you there aren't a lot of options for this disease.

Questions?

So as I said, there were many studies about this drug that looked at how efficacious it is and the last analysis we looked at people who responded versus folks who did not respond. The red ones are patients who received the Revlimid and had the response to it. The blue one are the ones who did not have a response and this is how many years did they survive. As you can see, the median survival for responders was about six years. For people who did not respond was 2.7 years. So definitely it makes a difference in how many years you're going to live if you respond to it and when I show you median years that means this is a halfway cut. So, you can do way better than that number of slightly worse. The worse number was 3 ½ years, but there are people who after many years of follow up they're still alive. So, you can have long term survival with this drug if you fall into that category of deletion 5Q.

So, if Revlimid didn't work your next options will be one of the hypomethylating agents. The Vidaza or the Dacogen. They are both the same group of drugs. We call them disease modifying because they are not your typical chemotherapy medications that we used to do for this cancer. They work on your cells that are stuck in the middle and help them reach that final goal of being a fully functional cell. So, we're not giving you a drug that's going to go and kill cells right and left, make you sick, throw up, etc. So, these medications are very targeted. They're working on the problem and the genes of those cells to help them mature and become fully functional. That's why we'll call them disease modifying. They're not cytotoxic chemotherapy and many of you who received this drug probably you'll get some fatigue, but it's not like you're slowing up or having diarrhea or getting very sick of it because it works different from other kinds of chemo. Same thing with the Revlimid. It's a targeted drug. You don't get too sick with it because they are not cytotoxic chemotherapy.

So, there are several ways you can get Vidaza. You can get it either five day. Typically the first study was seven days continuous each month. So, you start day one. For seven consecutive days you get the drug then next month the same thing and so on, but because most clinics are closed on weekends, we did more studies where well, let's look if you get five days on, you take two days off during the weekend then you take the Monday and Tuesday the rest of your chemo or even well, let's just try giving you five days instead of seven days. Pretty much the response rates are similar. Ideally if you can get seven days, it's better to get seven day, but we haven't seen a huge difference between those who got seven continuous days versus what we call it five, two and two. That's five days, two days break and two days versus five days and that's it. The response rate with Vidaza as you can see, this is a red cell transfusion independence is about 50 percent if you're taking the weekend off, 55 percent if you do in five days. It's about 60 percent if you doing the high dose five days. So, there was no difference between the three arms and the side effects are what most of you been through when you get this medication. It's a blood counts going to drop half ways through your chemo cycle. So if you're getting your drug today, 10 to 15 days from now the blood groups are going to go down. You're going to need more transfusions before you recover. Eventually, if you're responding for this disease your transfusion

requirements are going to go down nd this is what we're after here. That's blood cell transfusion independence.

So, the best results on average for what we say for low risk MDS if you end up getting a hypomethylating agents, the odds that you're going to be transfusion independent are 50/50 which is similar to what I've shown you was Lenalidomide, similar with Vidaza. That's why there are few options for the lower risk and there is a good response rate. The problem is when you fall in the high risk group of MDS. So, the way we approach high risk group of MDS the only cure for Myelodysplastic Syndrome… if you want to get rid of this problem there is only one cure. That is stem cell transplant. Everything else I'm showing you with these medications none of them is going to cure the MDS. They're going to give you more time. They might slow down the transfusion, but you're never going reach a point where you're going to sit here and say I am MDS free. If you're after a cure, the only cure is going to be the stem cell transplant and I'll touch base on that later, but if we have someone who's a high risk disease which I showed you this is a group of people whose survival is going to be anywhere from few months to year and a half, two years at most. We start looking for a donor for them to consider a transplant.

Who do we transplant? Ideally, if we're looking at age groups, we're looking at 75 and younger because this procedure is a little bit tough. So, most folks above 75 cannot handle transplant. So, most centers cut off at age 75. We make few exceptions here and there if you're like very active, very good performance status. You don't have any other medical problems we might consider a little bit older than that, but most centers going to look 70 to 75 as the cutoff. So, if you have a donor you go stem cell transplant and you're favorable which means you're fit enough and an age where you can handle this procedure. If you don't have a donor, the only option for the high risk group that's approved is the hypomethylating agent which is the Vidaza and the Dacogen. You can start with either one of them. Nowadays this is very, very unlikely to happen because we do a happen because we do a lot of what we call them half match transplants. So if you have a son, a daughter, if you have a dad, a mom, you have a daughter. Five, ten years ago we were only looking for fully matched donors and it was tough to find donors for everyone, but nowadays almost 98 – 99 percent of patients have a donor. So if you have parents or kids this technically means you have a donor. So, this is becoming less and less. As I said, most people will have a donors are going to move ahead to transplant. If you're fit enough and you're in the age group for it if you have a high risk disease.

Q9: How about sisters?

Melhem Solh, MD: And sisters are ideally… these are going to be a full match or a half match or no match. The odds of each one is about 25 percent. So, we type the siblings first. So if we're looking for a donor for a transplant, our number one choice will be a sister or a brother if they are a full match. If you don't have a full match sister or brother then we start looking at half matches. If it's your siblings can be half matches. Your son or your daughter or your parents can be a half match. So, this would be the second option or we look through our registry for a donor

if you have an unrelated person who's a full match for you, but following these algorithms, as I said, almost everyone have a donor at this point.

Q10: (inaudible 31:18 – 31:27)

Melhem Solh, MD: We don't like mismatch unrelated. Some centers do that, but personally and at our center we don't favor this because a long term side effects from that are much worse. The GVHD, we'll call it the graft versus host disease. Even if you do well from a cancer perspective, your lifestyle isn't going to be good long term because you're going to be dealing with some complications from the graft.

Q11: (inaudible 31:51 – 31:59)

Melhem Solh, MD: A related because we do them different. So, if you do them the same way, of course, the 50 percent is going to be a no-no, but because we do the transplant in a different way when we have a half match this becomes a better option because the way we go about graft rejection and the side effects of the transplant is slightly different. This will make the outcomes better.

Q12: If you're at low risk (inaudible 32:24).

Melhem Solh, MD: Well, there's a smaller group. So, let's say you're at low risk and you're requiring a transfusion every couple weeks. You've went through Revlimid, you've went through Vidaza and you're still requiring transfusions you have not responded. Your only option is going to be a transplant or you're going to keep getting transfusion for the rest of your life which is not a good thing because you'll develop high levels of iron and so on. So, very few group who don't respond and still requiring transfusions, transplant is an option for them, but in general it's mostly for the high risk or what we call them the Intermediate 2 risk group or if you're a very, very young person who's 30 – 35 year old who has a lower risk disease, was requiring transfusion definitely, we'll offer them transplant because transplant, as I said, can give you a cure. You can live pretty much the rest of your life without having to worry about MDS. Everything else as I will show you is going to give you… so for the high risk the Vidaza which some of you have been taking. It's seven days a week or you can take the five days. People who get it their survival is about 24 months, so two years. Compared to other kinds of treatment where the high risk disease was 15 months. So, it makes a difference, but it's no something that's making you live 10 years or 15 years. That's giving you more time and this difference was significant. So, we'll always look when we do studies like sometimes you're going to see a couple months difference or six months difference. Is it a significant difference between the two groups? So, this is one of our options for high risk disease if somebody cannot tolerate transplant or we don't have a donor ready yet .We need something to hold their disease before they become an acute leukemia till we bring them into transplant.

So as I showed the response rate is about 50 percent in the high risk group with Vidaza similar to what we saw in the low risk group with Vidaza. So it works. It's not curative and when we look at who is going to respond to Vidaza, it's definitely people who… if you look at these risk factors, so we look if you have a poor performance status which means if you're somebody who's sitting on the couch 90 percent of the time. If you requiring more than four units of blood every eight weeks, if your cancer cells are increased in your blood or if you have very poor chromosomes on your cancer cells. So, each one of those will bring your response down. If each one factor… the more factors you accumulate the less likely you're going to respond. So, someone who doesn't have any of these factors you can see how well they're going to do in terms of their survival. So, their median survival is more than five years. Somebody who has all these factors almost nobody made it beyond two years. So, these are things we always look at when we're choosing what kind of therapy, how long you're going to be on it and how fast we need to move with your transplant and so on.

Again, this is showing you the previous graph is if you have none of the high risk factors which means the chromosomes aren't too bad, if you're functional, you're not requiring a lot of blood, you're going to do much better with Vidaza than someone who has all these problems.

There were many studies done about this drug in high risk patients and they pretty much all showed the same response rate. So, anywhere it's from 40 to 60 percent. So on average when I quote somebody with the high risk disease except the very, very high risk group, we will say well, one options is if you want to consider Vidaza, on average people are going to live on it 18 to 24 months. Compared to other medications you're going to do… Dacogen is probably going to get you the same result. So as I said, they're interchangeable, but once you progress on one you're not going to get the same outcome from the second one. So if you're taking Vidaza and you stopped responding after 20 months and we switch you to Dacogen, you're not going to get another 20 months from Dacogen. You have already used that class of drug. So at best, you're going to get five – six months from the second hypomethylating agent and this group of people I will show you some of the data. Once you progress, it's not going to look good without… the only thing that can give you a reasonable result or a reasonable survival is going to be the transplant.

So, this is a Dacogen study. Same thing. It showed similar results about 30 to 50 percent improvement. So, 30 percent overall response improvement about 50 percent and the side effects of the drugs are very similar both of them. Both of them you're going to see your counts drop down. You might need some more transfusions in the beginning and so on, but they are not cytotoxic drugs. So, you shouldn't get very sick with these medications. You might have heard your oncologist telling you you have refractory anemia with ring sideroblasts or refractory anemia with excess blasts. These are terms we use based on what we see on your bone marrow. So if we see cancer cells, we'll call it the excess blasts depending on much cancer cells you have. If we only see some red cells with multiple dots in them we'll call it refractory anemia with ring

sideroblasts. We don't use this per se to risk stratify you. We use the score I showed in the beginning. We put everything together including this to give you a risk group.

So, and people will say that when they did the Dacogen study, I showed you with the Vidaza it showed a difference in survival between the two groups. The Dacogen study as you can tell their survival wasn't different between those who got Dacogen versus those who did not get the Dacogen, but the study was done in a weird way that included patients who are lower risk and so on. Most people who treat MDS believe the two drugs are going to give you similar results although the data didn't show that because the studies were done different, but there is no reason why same group of drug who works the same way to have different outcomes. So if you're getting one or the other, you're fine.

Q13: (inaudible 39:13) just for a second? Am I interpreting it right that supportive care is kind of just about as good as Dacogen?

Melhem Solh, MD: In this study. So if you do and as I said the problem with this study is that the first study they looked at Dacogen as they included patients who were lower risk, but if I have people with lower risk disease they're going to live three years if I give them Dacogen or if I give them Procrit or I give them blood alone. So, I'm not going to show a survival difference at three years in a low risk patient if you're giving them Dacogen or Vidaza or anything. The Vidaza study only picked up people who have very high risk disease. So, these are people who are going to die within a year two years if they're not getting active treatment and that's why we believe this study did not show a difference in survival in the Dacogen because it included lower risk disease patients. The Vidaza one did not include lower risk disease. As I said if you're getting one or the other, you're going to… if you're going to respond to a hypomethylating agent you will respond. We've had in our clinic people on Dacogen who are going on years on it. We've had people on Vidaza doing very well and we've had patients who doesn't respond to either one.

Q14: The first chart, the IPSS and the revised that was (inaudible 40:39).

Melhem Solh, MD: That's when you present.

Q15: So, the Vidaza added two and a half years (inaudible 40:46).

Melhem Solh, MD: So, from the time of presentation the survival was about 24 months. So when you come in with the MDS, at the point of diagnosis we give you that risk score. Are you a low risk, are you a high risk when you present.

Q15: That's two years you take Vidaza (inaudible 41:07).

Melhem Solh, MD: No. The Vidaza is what's going to make you reach that two years. So if you're a high risk and we don't treat you, it's about four or five months survival. So, Vidaza is pushing you to the two years.

Q15: (inaudible 41:21)

Melhem Solh, MD: If you're low risk, it's about six to seven years you can do okay with Procrit or Aranesp depending what's your requirement. If you're not requiring transfusions and you're a low risk you don't need anything. So, let's say your hemoglobin is nine and you're not needing transfusion, you're a low risk. I would just back off and watch you for… it might take a couple years before you even need blood. If you're needing transfusions, we start with the growth factors. If you have the deletion 5, you get the Revlimid and we escalate it gradually.

So, these are the results with each drug alone. Then we thought about why don't we try to combine Revlimid with one of these drugs, with the Vidaza or with the Dacogen? Can we get the better result in the high risk group and, again, there were a couple studies that were done about this topic where patients were given Revlimid for three weeks and you get your Vidaza for five days and this is mostly high risk MDS and we looked at the response rates. It wasn't that impressive in terms of the difference when you do Vidaza alone. People expected when we were going to combine the two drugs we're going to get a much higher response. It wasn't that different. So if you look at the complete response with about 40 percent, overall response in the 60 percent. Slightly different, but the problem when you combine the two drugs the side effects become more. You're going to require more transfusions during the cycles and we sometimes use a combination in somebody who is very, very high risk and we think we need to receive a response quicker and so on, but for the most part, we haven't had any convincing evidence that the combination is any better than one or the other.

So, these are the drugs that are most commonly used probably most of you is getting one or the other either the Procrit or Aranesp, Revlimid, Vidaza, Dacogen or sometimes Neupogen if your white counts are down you want to boost the up. There are plenty of medications been studied for MDS. None of them is showing to be a… the changing drug. The one that you're going to probably hear about soon as the oral Vidaza. So, it's going to come out in a pill form. At least the earlier studies are showing results similar to the old version of Vidaza which was the IV. So, it's probably going to take another couple years before we'll reach that point. It's been under studies, been going on in phase two studies. There are plenty of newer drugs that we use for other diseases we're trying in MDS. As you can see, the response rate is about 15 percent, 20 percent and so on. I think this is one drug that you're most likely going to see in the next year or so coming out to the market.

So, what happens after your fail Vidaza or Dacogen if you're a high risk disease? As you can see, the overall survival is not good. We're talking months here. So if you progressed on Vidaza or Dacogen, survival is anywhere from four to eight months and these are from three different

big centers – Moffitt… what's GFM? Sorry, forgot that and the MD Anderson. When we took a group of people who progressed on these drugs and looked at what they received afterwards to see how well they're going to do. So, this is a green line as a transplanted group. As you can see this is the only treatment after you progress that's going to keep you alive long term. Everything else, things are dropping down. Whether you get another hypomethylating agent, if you get a clinical trial, if you get chemotherapy, the only open at that point is if you want to be on this side often curve which means you're going to be alive seven – eight years after it happens, the only treatment is transplant. Ideally, we'd like to transplant you before you fail Azacitidine because your outcome is even better if you get the transplant before you fail those medications. So, people who get transplant for MDS today, if you're a high risk MDS you get transplanted today your odds of being alive long term are at least 50/50. If you're high risk MDS and you don't get a transplant, your odds of being alive five years from now is probably 10 percent. If we wait till you fail Vidaza and we transplant that 50 percent chance drops down to about 30 percent chance. So typically, we'd like to see you before you have progressed in all these medications so we have a donor in line and we're going that route.

Q16: Can I ask you a question about that? (Inaudible 46:33) you had a transplant 50 percent what's the survival in years?

Melhem Solh, MD: Well when we do a transplant, we look at five years cutoff, but if you're alive five years out from transplant, you're going to live way longer than that. Most people who relapse or die from transplant is going to happen in the first three to five years. So if you're past that five years and you're still alive, the odds that you're going to be alive at 10 years and 15 years from the transplant become 90 percent.

Q16: You're saying 50 percent survival at five.

Melhem Solh, MD: Yeah.

Q16: (inaudible 47:12).

Melhem Solh, MD: Yeah, but as I said. We do only five years because we don't keep following you forever, but if you made it to five years then you're going to be okay.

So, this was another analysis of people who failed Vidaza with high risk MDS. So, the two year survival if you failed it was 15 percent. So about one in 10 people can make it two years after you progress and Vidaza and the survival, the average survival, was about six months for everyone.

Q16:The same as Dacogen?

Melhem Solh, MD: Yeah. Same thing.

Q16: What about the Aranesp?

Melhem Solh, MD: Well, that's a different story because you haven't gotten the Vidaza. You haven't gotten the Dacogen. You haven't gotten the Revlimid. So, there is still… depending on your disease risk. So if it's a low risk, you're still fine. If it's a high risk 1) I probably wouldn't do Aranesp, I would jump to one of those right away, 2) is you need to get started on one of these drugs if you're high risk disease.

Q17: I have a quick question (inaudible 48:20) Procrit and (inaudible 48:26) injection (inaudible 48:28) and that did not work. Is that a predictor that (inaudible 48:38) would not work the same 50 percent (inaudible 48:45)?

Melhem Solh, MD: No. It depends how much blood you're needing in a month. So, the predictor is the amount of blood transfusions you're requiring. If you're getting more than four units in a month, your response is going to be lower. If you're requiring less than that, you should fall in that 40 to 50 percent range and remember that's an overall response. So, sometimes what happen is you're not going to become transfusing independent, but instead of needing four units you'll become needing two units a month. So, it'll make some improvement.

This is similar study showing the difference in outcomes after you fail the hypomethylating agents. Again, the yellow curve here is the allogeneic transplant. These are either other drugs or clinical trials or chemotherapy. So, definitely that's your only salvage once you progress on the hypomethylating drugs.

So, talking about transplant for MDS. Problem with transplant for MDS is many patients are above that age cutoff I was telling you about and that age limit keeps changing. Like 10 – 15 years ago we used to stop at 65 years. Now, we're up to 75. The brave ones of us will go 76 – 77. So, many people with MDS are above that age limit. So, transplant is not even an option for them. As I said, the long term can reach 50 percent. Even with transplant you can still see MDS come back. The odds of that happening if you're a very high risk disease is about 20 to 30 percent. That's why not everybody is alive five years from now. It's only 30 to 50 percent is because there is some chances that the disease can come back and there is a chance that the transplant itself from complications can take your life.

So, a few things when you come for a transplant consult we look at and we usually think out loud in front of you is let's say you have 15 percent cancer cells in your bone marrow. So, our goal is to reduce that number before we transplant you so you can get a better result from the transplant. So, don't be surprised if you walk into a transplant consult and we say we want you to go back and get some Vidaza or some Revlimid for a few months and then come back to transplant because the less number of cancer cells you have at time of transplant, you're going to do better. Two, is how much… what intensity will cause the conditioning regimen is the chemo that we

give you just before we give you the cells from your donor and we can go because there are two types of transplant. There are something called mini transplant and there's a full transplant. So mini transplant if you're above a 60 or a 65 that's we're going to use for you. So, we don't give you too much complications from it and the full transplant if you're younger is an age 60 or 65 and the only difference is how intense is the chemotherapy you're going to receive before you get your cells.

Q18: Can you tell me what (inaudible 51:58).

Melhem Solh, MD: In general it's 60, 60 years. If you're above age 60 years, you'll get mini transplant. If you're younger than 60, you'll get a full ablative transplant. Yes, go ahead.

Q19: When you say mini transplant (inaudible 52:15) comparing that to a full (inaudible 52:18).

Melhem Solh, MD: So it's based on… so back in the days as I said, two years ago we were only stopping transplants at age 60 to 65 because what we didn't know very good is transplant the way it works is not just as a chemotherapy would give you before the cells. The reason you can have survival for many years, let's say, I get the cells from your brother or your sister is your donor cells are going to circulate in your body 24/7 and they're going to attack any MDS cells that you're going to make. So, the reason you have that long term survival is because of the cells not because of the chemo. So, we've learned is all we need sometimes is actually just to suppress your system little bit, so we can give you these cells and let them do their job. So, that's what mini transplant is. We're not giving you a very intense chemotherapy to kill all your MDS. We're giving you chemotherapy to kill your immune system, so you don't kick out these new cells and let them do the job for you. So, the outcomes have been shown to be almost similar, but we… you'll do slightly better with the ablative transplant with the full transplant because yes, you're getting more chemo that can help, but with the reduced intensity you're still falling in that 30 to 50 percent range. So, myeloablative I would say your odds are going to be 50 to 60 percent. If you're a mini transplant, you're looking about 40 percent.

Q20: (inaudible 53:52 – 53:57).

Melhem Solh, MD: Yeah. By itself is not ablative. So, we're not using that chemo with a goal in our mind that's going to kill whatever MDS you have left, but if we're doing a myeloablative which is a full transplant. So, that will kill the MDS cells.

So, the finding in transplant is when is the right time. It's always probably you'll go around. You're going to hear different opinions, but one thing we'll all agree on is if you have a high risk disease the timing is when you show up with… they cleanse your cancer cells a little bit, we take you to transplant. If you're intermediate risk and you're an older age group, usually people don't do as well. So, we will advise for transplant. If you are a low risk, we can watch and wait and

you're going to need transplant at one point, but it's not going to be today or next year. Maybe three – five years down the road.

So, what's cooking in MDS? There are, as I said, one drug that you're going to hear about in the next year or so is oral Vidaza which is oral Azacitidine and the data from this one is showing safety patterns similar to what you see with the IV Vidaza. So, you're going to be switched from getting the injections to just getting pills and it's given for 14 to 21 days every four cycles. So, it's similar to Revlimid if any of you have taken Revlimid before. Results are shown about 50 percent response rate in the earlier studies and as I said the safety profile is similar to the Vidaza that we give as injections.

So this is one drug you're going to hear about which is oral Vidaza. The other drugs that has been studied is called Vorinostat which is a… it's a group of medications we'll call them histone deacetylase inhibitors. There are studies going on. So if you're somebody who has progressed on all these medications, you're not interested in transplant, clinical trials is the option. Unfortunately, we don't have medications, clinical trials at our center for MDS, but I know Moffitt has some, MD Anderson has some clinical trials for high risk MDS who have progressed on hypomethylating agents. As I showed ou the graphs before, once you progress, you're going to get little bit of a response on whatever you try. The odds are about 10 to 15 percent that you're going to respond and there are many medications that are being hacked. The Vorinostat combination with Vidaza showed this was for people who are up front showed similar response rates to what we see with Vidaza alone slightly better, about 50 percent. So, we don't use this combination as a standard of care. Outside of a study, we still don't use it. So, the survival you see here you might be impressed. It's about three years, but this included people who are very low risk and low intermediate risk. So, we always when we look at studies we have to look which patients did they treat? Are they the high risk group or does it conclude some good risk ones to make the number look better?

So, the last topic I want to touch on is iron chelation. For many of you who are on transfusions on a regular basis, blood transfusion by itself is risky. One, there is a risk of contamination of the blood unit you get. There is a viral infections, a risk of bacterial infections, but the long term risk is iron overload. So, we know this from patients who had thalassemia, who had sickle cell who need transfusion that there's get iron overload eventually the higher levels of iron are going to deposit in your organs, your liver and your eyes. They're going to get into troubles from the iron overload and the more we study the future the more we knew that by itself was the iron level can you make you live less compared to somebody else who we are trying to keep their iron level at the lower side. So if you're someone requiring transfusions on a regular basis, let's say two to four units a month, that's something to look for. The iron level and what we call iron chelation. There are medications out there that will keep your iron level down although you're getting a lot of transfusions. The reason is that when we looked at two groups of people those who got chelation, the green curve and the patients who did not get iron chelation. That's the blue curve. So in other words this is somebody who has been getting transfusions for many months and we

didn't do anything about it. This is a patient who we have iron chelation to keep their iron level less and they have the same MDS, they have the same risk and same everything. The one who gets iron chelation will have a better survival than the one who does not. It's not just the iron by itself. A lot of us believe the high iron is a marker of inflammation and so on. That's what makes you live less. So, there is oral pills for iron chelation. There's a drug called Exjade. There is IV or sub cue form. There is Desferal. So, there are so many ways your oncologist can monitor your iron and keep that level down and this is something that should be considered if you've been getting transfusions for a long time. The other thing we don't like about high levels of iron is when we take you to transplant if you have very high iron levels your outcome is slightly worse than somebody who had their iron level has been under control. We don't try to bring it down before transplant because it takes time bring the iron level down. So, it's always best if you start it when you're getting your transfusions.

So, this is… as I showed you so you live longer if you have iron chelation, but then the question was do you live longer because the iron is giving you a problem or because your MDS is becoming acute leukemia. So when we look at the two groups, actually they progressed to acute leukemia at the same rate. So, the reason you're not making… you're not living enough is because of the iron giving you problems. It's not because your disease is killing you. So, that's something if you've been getting blood for a long time, bring it up with your oncologist say do I need to watch for my iron level? Do I need iron chelation and so on and most people tolerate these drugs very well.

So in summary, MDS is a heterogenous group is it just one disease, but as I showed you in the beginning you can have a lifetime survival from a few months to many years. The risk scoring and the risk categorization is very important when you present. The only cure is transplant whether you're a low risk, intermediate risk, high risk, it is transplant. We advise transplant for intermediate and high risk because the transplant itself is a risky procedure. So if you're a very low risk who's going to live seven years, I'm not going to put you a procedure just has a 10 – 15 percent chance of taking your life in the first year. So, we will wait on transplant till you become a higher risk, but if you're somebody who's also living for one year as 10 percent, definitely I'm going to put you through that procedure to give you that 50 percent chance of being alive long term. The approved the drugs, as I said, are the growth factors which is EPO, Aranesp, the Revlimid, Vidaza and Dacogen and there are clinical trials going on. I think the most active one is going to be the oral Vidaza that you're going to be hearing about.

Questions?

Q21: Now, you're saying that (inaudible 1:02:12) and you're on four units a month taking medication for the iron overload what's your (inaudible 1:02:31)

Melhem Solh, MD: So, have you… no, if you're just on… because you don't want to continue transfusions. So, you're going to always need something to come off the transfusion. So, your options is Revlimid, Dacogen or Vidaza and you're still needing four units a month?

Q21: (inaudible 1:02:52)

Melhem Solh, MD: Then you need transplant because you cannot live on transfusions forever. You're probably… how old are you now?

Q22: (inaudible 1:03:03)

Melhem Solh, MD: Okay. So definitely transplant is a way to go at this point if you've gone through all these medications.

Q21: (inaudible 1:03:10 – 1:03:19)

Melhem Solh, MD: Exjade. So you have… some people with low risk as I showed you not everyone with low risk will respond. It's about 60 percent response rate. So, you're falling in that group although you have a low risk, but you're not responding and you're still requiring the transfusion. So, the transplant you're going to have because we're not worried about you becoming acute leukemia, but we're worried about your transfusions to be continuous. That's what's going to run you into trouble and you cannot live on transfusions many years.

Q23: My blood's getting lower and lower (inaudible 1:03:52).

Melhem Solh, MD: One thing is they have to repeat your bone marrow biopsy if they haven't done one lately to see how you're progressing. Are you still low risk? Have you become a high risk and so on?

Q24: (inaudible 1:04:07)

Melhem Solh, MD: So, one thing we worry about is like have you progressed over time. I don't know when was your last bone marrow biopsy. Is that one thing to look at?

Q23: So definitely, that's a starting point plus if you've gone through all the medications, you're still needing the blood, you're still 62. So, transplant is your route.

Q22: Thank you.

Melhem Solh, MD: Go ahead.

Q25: Our patients (inaudible 1:04:42) at what point (inaudible 1:04:55) oncologist (inaudible 1:04:55)

Melhem Solh, MD: So, you start running into iron problem once you've gotten 20 to 25 units of blood. So, if you've crossed that number in the past year or two that's when… They can check the iron level in you. It's called ferritin. It's the iron store. If that's very high they can consider starting it.

Q25: (inaudible 1:05:16) give my husband (inaudible 1:05:20 – 1:05:25)

Melhem Solh, MD: Usually once you're above... the ferritin is above 1,000 that's when we start considering the chelation.

Q26: (inaudible 1:05:35 – 1:05:42)

Melhem Solh, MD: Well, haplo is one of the allogeneic transplants. So if you're getting a myeloablative, a full intensity, it's similar.

Q26: (inaudible 1:05:51)

Melhem Solh, MD: Yeah, it's similar if you're getting a full intensity. We looked at this in our center because the thoughts has always been well is there a slight increase in mismatched transplants, relapse rate from a half match sibling, but if you're getting full intensity it's the same like the full match.

Q27: (inaudible 1:06:09 – 1:06:15)

Melhem Solh, MD: No. Well, some people who get Vidaza interrupts the treatment like your cancer cells can go up a little bit, but you go back on the medicine and you're reassessed. I said all these medications you want to give it at least three months before you say oh, it's not working because these are not toxic chemotherapy. So when we give somebody toxic chemo, we're going to see a response in three to four weeks. When it feeds a biopsy you either responded or not, but with Revlimid, Vidaza or Dacogen that's not going to happen this way. It's going to take on average about three months to see the further response. So, you have to push through these first three cycles to see how you're responding or not.

Q28: (inaudible 1:06:58 – 1:07:03)

Melhem Solh, MD: I usually recommend it once a year if the counts are stable, but any drop in the counts, any change in the blood counts that's a reason to do the biopsy sooner.

Q29: If you're a low risk and you're responding to Procrit and no blood transfusions you just want to watch.

Melhem Solh, MD: As President Bush says, "Stay the course."

Q29: … I was going up and up…

Melhem Solh, MD: But it's like anything else we're going to do what are we going to try to achieve? If you're not requiring transfusions you're doing well like I can do more aggressive stuff to you, but the end result is you're not going to require transfusion which you already have it. So yeah, if you're low risk you're responding to Procrit I wouldn't change anything.

Q30: (inaudible 1:08:08) it was my understanding if you're Dacogen in approximately 80 percent of the cases, within 30 days or so within the first two cycles if you were getting it every fourth week (inaudible 1:08:24) is a positive reaction we'd know within about 30 – 35 days.

Melhem Solh, MD: That's a little bit too soon. You have to… it's usually the third… you have the median time to response is like so when we do a study and we give people medications we're looking at when you're having a study they're probably doing biopsies every month or every couple months and when they come out with the results they look at something called median time to response. So, how long is it going to take you if I start you on treatment today how long is it going to take half of the patients to respond? So with the hypomethylating agents, you're looking two to three months. So, you're going to need at least two cycles before you recheck to say are you responding or not. Some people even argue you have to do four cycles before you say somebody has progressed because this drug is not going to work right away. It's great if it does, but if you're… let's say you're required four units this month you'll get first cycle of Dacogen. Next month you require four units that doesn't mean you have not responded to Dacogen. It means we haven't had enough time to know if you're responding or not.

Q30: Thank you.

Melhem Solh, MD: You're welcome. Any more questions? Go ahead.

Q31: I've been on Vidaza for years and they stopped (inaudible 1:09:53) everything was level and because of my age (inaudible 1:09:59) take a break and see what's happening next. Now when they stopped the Vidaza, they advised me to stay off alcohol and now again because of my age I see that they say moderation it's okay. So again because of (inaudible 1:10:24) how many martinis…

Melhem Solh, MD: Are they chocolate martini or which kind of martini you drink?

Q31: Only straight up and seriously one of the questions about the St... not St. Joseph but the Northside Hospital (inaudible 1:10:50) very close to that operation. Is that operation a Northside operations?

Melhem Solh, MD: Yeah, there's a Northside. It's all the same system.

Q31: And I guess that's (inaudible 1:11:09) the only thing I can say that some of my fellow MDS (inaudible 1:11:15) I'm 90 years old and…

Melhem Solh, MD: Then go ahead and have a martini (laughing).

Q31: That's all I have to say.

Melhem Solh, MD: How long have you had the MDS for?

Q31: I was diagnosed with anemia first. I've been a patient at the veterans hospital for about 15 years before the present situation and they diagnosed me with anemia first. That was almost two years and at that point they tell me oh, don't worry about it. Don't do anything until routine bloodwork and then they diagnosed… They did this bone marrow (inaudible 1:12:12) so they were treating me for (inaudible 1:12:16).

Melhem Solh, MD: You're not needing transfusions now.

Q31: (inaudible 1:12:21) no. Again, I've had other problems but they keep saying because your age nine times out of 10 you got a new doctor (inaudible 1:12:34) Oh, you're still here?

Melhem Solh, MD: Well the thing is we… they should look at what we call the physic it's not the number of years… it's like how active you are. You can be 90, but if you can tolerate the drug fine and your responding to it that's definitely something to consider because if you don't have a bunch of other medical problems that you're dragging behind you means your survival is going to be based on your MDS. Sometimes we worry about age like I'll have people in their 60s who have 10 medical problems. I know they're going to die from something else in the next couple years, so why to put them through aggressive things for the MDS? But if you're not requiring transfusions and you did okay, it makes sense to take a break and you can have a martini here and there if your platelet count is not too low.

Melhem Solh, MD: Thank you. Thank you, everyone.

(Applause)

Rebekah Barr: Good morning. My name is Rebekah Barr. I'm a leukemia coordinator at Northside Hospital. We see patients who have MDS, leukemia, lymphoma and related diseases

and I work with Dr. Solh as well. I'm going to talk to you a little bit about *The Building Blocks of Hope*. This is the material that you got when you came in, that three ring blinder, if you wanted to pull it out and take a look at it as we go. It's not going to be a one to one alignment, but some of the materials we'll talk about here are in that binder as well.

So, this is called *The Building Blocks of Hope*. It is a patient and caregiver guide for living with MDS. This is created by a multinational nurse leadership board for the MDS Foundation. So the goal is to answer some of the coming questions that people have been diagnosed with MDS have about their disease starting with understanding the diagnosis of MDS, how is MDS diagnosed, what are the treatment options, common side effects of treatment and symptom control for those side effects, treatments that may be on the horizon, the consequences of blood transfusion and the iron chelation that Dr. Solh talked about is related to that question, selecting a bone marrow transplant center for people for whom that is the indicated treatment and keeping yourself healthy in general and Dr. Solh did go over a lot of the background stuff for that. So, I'll just go over some slides that give you a different look at it so that you can find those materials when you want to go back to it later.

So, some of *The Building Blocks of Hope* are understanding your disease and that's understanding how it caused as Dr. Solh went through. Knowing your IPSS and the IPPS-R risk categories for treatment decisions. Being an active participant in your treatment. So, ask questions about your options, what kind of schedule is involved, the possible side effects of the recommended treatments, strategies for managing your side effects and consider with any treatment you're going to have lifestyle changes, things to consider such as transportation, working and caregivers. Ask for help. There are resources such as the MDS Foundation. There may be local support groups in your area as well. So, this is all components to help you build a plan to track your progress through your treatment.

So reviewing again, the MDS is a group of blood disorders, heterogeneous meaning that they're not all exactly the same. They may behave differently. Variations in clinical findings. That's your lab results, your trajectory. That would be the prognosis and the treatment recommendations which are based on the indicators that have been discussed.

So with MDS the cells do not develop properly. You'll have abnormal size and shape which is called dysplasia and when the cells are abnormally shaped they don't function properly. You don't have the ability to fight infections because your white blood cells are not fully mature as well as your red blood cells and your platelets and so these cytopenias will result in the low blood counts and for most people that's the first thing that is an indicator that something is going wrong. They've been to the doctor and they've gotten the CBC and the counts are down and need to be investigated further. There is that risk of developing leukemia. The leukemia transformation as the disease progresses and generally speaking as the disease progresses, the bone marrow function declines. This chart just shows you the development of normal blood cells. So, this stem cell is the source of all of your blood cells. It will respond to different signals

and then develop into all of these other kinds of mature cells which have different functions in your body. In MDS, it's the myeloid cells that are misbehaving and so your neutrophils, basophils, eosinophils, these white blood cells as well as monocytes, (inaudible 1:19:12) platelets and red blood cells will be affected.

So, you'll see here that when you have MDS these immature precursor cells build up. The development gets stuck at this phase and you lose the development of these fully matured cells and then since the cells are stuck here and do not develop into these final forms, you have peripheral cytopenias meaning low white cells, low platelets, low red blood cells and those are what give you the symptoms.

So, diagnosis. Most of you are pretty familiar with this already with the peripheral blood counts. The bone marrow biopsy is the definitive diagnosis and then some other tests that can tell us a little bit more information about the status of your disease. These additional tests may be ordered to rule out other forms… other causes of anemia and then, again, would be categorization. The WHO criteria, the ones that are more commonly use now, the FAB is an older one. The IPSS and the IPSS-R are for determining the disease trajectory that's predicted based on how your disease presents. Dr. Solh had a nice slide about that, the factors that go into determining what exactly your IPSS score would be. Just to summarize, the main things we're looking are your blast percentage, the cytogenetics, your blood counts. The IPSS is important because that determines what… how you should be treated if you should be getting more intensive treatment earlier or if a more moderate treatment will be more appropriate the stage you're at and this is a website, the MDS Foundation website which you probably familiar with that actually has a calculator that you can put you own particulars into and determine what your IPSS score is and this is the website for the organization that it's created this for.

Q32: (inaudible 1:21:50)

Rebekah Barr: I believe it is. If not, you can go to the MDS Foundation and it's on the website there.

So, the average age of diagnosis of MDS is 73 and as Dr. Solh said it is incurable for most patients with stem cell transplant being the only real possible cure. The leading cause of death is the disease itself with 80 percent of patients who are diagnosed dying from MDS rather than from other causes and those risk stratifications are important for deciding what the best treatment options are.

So as I said, MDS is heterogeneous. Everyone has a different presentation. All of their risk factors are different and so the treatment is going to be individualized as well. Some of the triggers for deciding to start or to switch therapies may include transfusion dependence, progressive cytopenias or increase in the symptoms associated with the cytopenias, increasing

blasts and the high risk disease as Dr. Solh reviewed talking about the cytogenetics that can be associated with some of the presentation.

Other factors that go into choosing treatments are your performance status. Are you in relatively good health before you were diagnosed? Are you able to do most functions for yourself and take care of yourself well? Comorbidities. Those would be your preexisting conditions, any diseases that you had before you were diagnosed that may complicate your treatment. The IPSS score stratifying you into the low risk or the high risk. So for low risk people, the idea is to improve your ability to produce blood cells. That's hematopoiesis so that you can remain symptom free and proceed with your life as normally as possible. For people who are in high risk, you know that the risk of evolving into leukemia and of death in the shorter term is much higher and so for them the critical goal of treatment is actually survival and prolonging life.

There are two types of MDS, primary and secondary, and that some people may develop MDS for no known cause and secondary where the MDS is thought to be associated with things such as prior cancer treatments. Secondary MDS is going to fall into your higher risk stratification.

The cytogenetic status and Dr. Solh talked about the deletion 5Q and the Revlimid being an option for those people. People who have a lot of changes in their chromosomes will also be considered higher risk initially and then lifestyle and lifestyle goals are also important factors in making those treatment decisions. The treatment options being transfusion and growth factors. The Revlimid, Vidaza, Dacogen. For people who are higher risk and maybe looking to transplant we may get into real chemotherapy such as Cytarabine, Clofarabine, Etoposide and ultimately stem cell transplant and there are always investigational studies going on.

There are at the time a fairly limited numbered of FDA approved agents and so we want to make sure that you get as much effect from each agent that you try before you move onto the next one because once you've stopped one agent and moved on, you can't really go back.

This is just a summary of some studies that are out there, some different targets and therapies that are being considered just to demonstrate that there is a lot of research ongoing.

The only potential cure, again, being transplant. For patients who have multiple comorbidities transplant may be more complicated. Dr. Solh did talk about donors being more readily available now that we are using half matched donors, the haplo transplants as they're called. Age alone should not be an exclusion factor for therapy because we want to consider how the patient actually lives their life, their comorbidities and their activity in their general life. We want to make sure that you take the time to let the treatment to run its course and make sure it's going to work before you give up on it. Blood counts will often get worse before they get better. So an increased transfusion intensity does not mean that you need to give up on your current therapy plan and so that early management of side effects may help you stay on the therapy a little bit longer, so we can give it a real chance to take its full effect.

This section is just going to describe why that time element is important for making sure we've fully evaluated the therapy. So before your treatment begins, your blood counts are going to be low. That's how MDS presents. Your normal cells are crowded out by those abnormal blast cells that we showed you earlier. So when you start your treatment the treatment is going to clear out those blast cells and frequently patients will also lose whatever normal cells they have during the course of the treatment, the goal being to get rid of the bad cells and then those good cells are sometimes the bystander of the effect. So you can see here six weeks into treatment a drop in the counts.

So as your bone marrow begins to recover from that treatment, there's room for the healthy cells to start growing again and as those healthy cells start to grow again, we expect a rise in your counts and hopefully with that rise in accounts an improvement of the symptoms as well and then as your counts rise, the hope is that you can be weaned from your transfusion support and begin to be more independent of them.

So, this first few cycles can be challenging. You can have early symptoms including the increased need for transfusion and other people may have other assorted side effects that go with the treatment. Book three in your binder there is (inaudible 1:29:12) the side effects and we're going to talk about that in the discussion part of this forum after lunch.

Key principles. Remember to give time, a minimum of four to six months is recommended to fully evaluate whether the therapy is going to work for you or not. The cytopenias can get worse before they get better and that can include increased transfusion support during that interim period and there are strategies that may be considered to help you get through those early cycles including dose modification, supportive care for side effects and just knowing before you go in what to expect. (inaudible 1:29:59) help people to get through those harder parts.

This is just an example of an actual patient's lab results through the treatment process. So, you see here when they're first referred for diagnosis the white blood cells, the platelets, the hematocrit are all quite low. Cycle one, cycle two, cycle three and cycle four of Vidaza. You can see the counts going up and down as they go through the cycles. Cycle four here you can see here they're starting to get some platelet response. In this person's case they actually got a transplant here after cycle four and 100 days after treatment all of their counts are quite dramatically improved.

This is a patient who's been on Revlimid for 10 years. So, they've got sustained cytopenias, but they're moderate and the patient is asymptomatic. So, they've got a lot of variation in here, but this is a level in which they're able to become comfortable and to maintain a pretty regular lifestyle.

Staying healthy. There's some of the stuff is covered in book four of your binder there. Talking about balanced diet. Daily activity and exercise. You want to stay… make sure that you're staying active and keeping up your strength during the treatment. Avoiding infection. So since your white blood cells are not working properly, you need to make sure that you're minimizing your risk of getting sick because you're particularly vulnerable for germs. Avoiding bleeding. If your platelet counts are remaining low, you need to take extra precautions to avoid things that could cause bleeding. Continue to enjoy the things that you love because this is a long term process and you need to make sure you getting as much enjoyment out of your life as you can. Getting enough rest. Taking advantage of available resources. So, we would refer you back to the materials you got as well as the MDS website. Asking for help when needed and being an active participant in your own care.

This is a Healthy Body Healthy Mind website that can give you some tips and this is about building your MDS plan. This is focused around The Building Blocks of Hope program. You've got the printed materials. There's also online materials that you can use in conjunction with this. So, the website is interactive. You'll find the entire handbook in the website as well with all of the figures and pictures. There's videos and slide presentations as well that can supplement the materials you've got. There's a search function that can help you find what you're looking for a little more quickly. Patient and caregiver resources are included in hyperlinks in the text and you're able to create your own handbook by putting… printing individual pages and putting your own information in there. So, this is a working document that you can do on page 92 to 98. You can put in components of your own situation with your diagnosis, your profile and your healthcare team and then tools for tracking your progress are on page 85 through 91. You can put in lab results, radiology results, other information that you might want to have at your fingertips. This would be a good place where you can keep track of your transfusions so that you can have an indication of if your transfusing needs are increasing. That can be a component in treatment plan and you can also save it as a PDF if you want to put it on a Kindle or an iPad. There's a patient liaison variable for you. You can call toll free or you can E-mail at any time at the MDS Foundation and, again, these are the tabs that you'll find in the book. Book one is called Understanding MDS. So, that's the disease process. Book two is Seeking Treatments, different types of treatment, modalities that are available. Quick tips on page three are the symptom management guides. Page four, the iron overload section and page… tab five is the My MDS Plan which is your workbook and then tab six is information about the MDS Foundation itself.

So, the rest of this program is designed to be a little more interactive for you guys to talk and share your own experiences and talk to each other about what has helped you through this process whatever bits of information you think you'd like to pass on that might help another patient or another family. If you wanted to start, if we could maybe go around and have people introduce themselves and talk a little bit about how they got here. If you don't want to talk that's absolutely fine as well. Anyone want to start? Start over here.

Q33: (inaudible 1:36:04) Dr. Solh recommended (inaudible) a haplo match and so my son is going to be the donor and (inaudible) transplant (inaudible) for June 1 and when they did all the tests and everything they found some infection (inaudible) so the transplant has been postponed. So now she's getting treatment (inaudible) and (inaudible)

Q34: I was diagnosed a year ago August. My oncologist has not really given me any kind of treatment at this point. No transfusion. I guess Vidaza is, like you said, they look at down the road, but he said let's hold off until we need to do that. I'm just curious about symptoms that other folks are experiencing. I don't know that's talk about that now or the next session, but just the…

Rebekah Barr: We'll talk about it a little more after lunch.

Q34: Okay. Yeah. So, I'm just hearing different things. I'm curious if folks are experiencing the same. So, this has been real informative to me.

Q35: I wasn't completely clear about some of the very end of his presentation because transfusions… not transfusions. Stem cell transplants, they recommend you do before you're 65, but if you're 62 and you're mild then your window of opportunity is three years. So but then I also heard him talk about 10 to 15 percent risk. So, it's kind of like you're not (inaudible 1:38:28) to balance what I'm hearing. So, do you get a second opinion at some point when you're reaching near the age of 65? (Attendee)'s not taking any kinds of drugs because he hasn't needed to and he hasn't done any kind of transfusion, but you kind of feel like you wonder if your approaching that age if you miss your window of opportunity if that's the age that beyond you don't really consider doing a stem cell transplant and he was winding up, so I didn't bother to ask him at that point. So, I don't know if there was a time issue, but...

Rebekah Barr: Well, the age that transplant can occur at will vary from center to center. Dr. Solh was saying that in his (inaudible 1:39:17) he'll look at someone 70 to 75 if they're in good health. So, that line is not written in stone. It moves. It is our experience with transplant changes it used to be 50. So, it goes up and it's very patient specific as well.

Q36: It is my understanding (inaudible 1:39:42)

Rebekah Barr: Right and so…

Q36: You got a low risk.

Rebekah Barr: Right and so you want to balance your risk and your benefits.

Q36: (inaudible 1:39:51)

Rebekah Barr: Right because there is the risk for the transplant itself being a cause of death for the patient and so if the MDS is in a lower risk status right now where you're not even needing transfusions, you don't necessarily want to take on that extra risk of the transplant.

Q35: So basically, you're going to wait until you're more classed to intermediate stage?

Rebekah Barr: Right to wait and watch it and see what happens.

Q35: Is that the point where you would ask your doctor for a second opinion or it seemed to me like your oncologist was the one that recommended centers that do transplants.

Rebekah Barr: Right. Yeah. Usually it's the oncologist who will recommend you to a transplant facility. If you're not feeling confident about what you're being told then by all means get a second opinion because you need to feel comfortable with what your treatment plan is.

Q37: My name is (Attendee) and I live Hiram, George here in the Atlanta area and last year in May, the end of May, my husband passed away of bladder cancer and I was grateful to see him to his eternal home because his first wife of 16 years and our marriage was 46, had passed away of breast cancer the year before I taught his little girl and became mom to 10 and 12 year olds and I had never feared cancer. Both of my parents had severe mental illnesses and I certainly was more frightened of that, but I was not somebody that neglected myself. As a public school teacher I had to get each year a physical from age 21 to 70 when I was diagnosed. I had a physical each year and I have my blood records, my CBCs from 1988 on (inaudible 1:41:49), but I am high risk. I'm high risk RAEB-2. I had 14 blasts. If you know anything about the blasts in 19… after 19 becomes leukemia. My second of four biopsies since last actually August when I had my… or heard the word MDS on August 22 and had a confirmed diagnosis on September 11 which is more than easy to remember, but I have had other bone marrow biopsies and my blasts were down to four on the second one. So, I have been to Northside and Dr. Morris is a wonderful doctor and he talked for… I had a three hour appointment with three relatives with me and he said he would push me more toward a transplant were I 40 years old and we have a young man in our church who is 49 and nine years ago of all people, Dr. Morris, did is transplant. It's been successful and he has comorbidities, diabetes and other things I do not, but at this point I have great peace not wanting to go transplant. I've had nine sessions of Dacogen. I'm on a break now and going to see Dr. Morris who is my second opinion. Everything I've studied says get a second opinion and I thought when I declined a bone marrow transplant at 71 now, I thought that I'm just not a gambler for one thing. I go with the percentages and I say if you're not part of the good percentage, it's 100 percent for you in the other direction, but I'm going back to him August 25 to further consult because I ask him what is my prognosis based on my diagnosis at this point which is right before transformation into leukemia. I asked him well, what is my prognosis and he said, "Six months to a year and a half without treatment." So, I have had treatment and I plan to continue treatment and I happen to have met a lady at another conference who at age 46 with two teenage children was diagnosed with low risk and when I met her she was a 26 year survivor

having been given two years to live. So, I say it's in God's hands and my husband before he passed away said, "When it's your time, it's time," and I feel highly blessed because I've got great support from family and friends and power of prayer to me means a lot.

(Applause)

Q38: I'm (Attendee) and (inaudible 1:44:58)

Q39: (Attendee). I'm from Jacksonville, Florida and I've been diagnosed well over a year ago low risk and I bruise very easily which I don't like, but they have not given me… the only thing they've given me was two (inaudible 1:45:21).

Q40: I'm (Attendee) and I'm from Birmingham, Alabama. I was diagnosed in January of 2008 with low risk MDS. My transfusion started in June of 2008. It was like once a month. Now, it's every two weeks and I've tried all the drugs that he mentioned and nothing's worked. So, I guess the transplant's next. I have been putting it off, but it's obvious I'm scared of it. Hopefully, I'll get more information and I do have the iron overload. He said it should be under 1,000 and mine's like 2,500. It was 5,000 at one time, but the more transfusions you have the more iron you're going to have.

Q41: (inaudible 1:46:36)

Q42: (inaudible 1:46:47) I'm from Georgia and I've been diagnosed with MDS since November 2011 and currently they treat me with Aranesp 500 milligrams every three weeks, but this past month I didn't have to have it. I had got bitten by a tick and was sick in the hospital three nights and three days and my white count just went way down and my red count went up. It was kind of crazy, but I still hadn't regained my strength. I've just been totally tired, exhausted. Just felt really bad, but I wanted to be here today to learn what I could about it.

Q43: My name is (Attendee) and I'm from Birmingham. My husband was diagnosed with MDS in January. Routine bloodwork. He went to the doctor for bronchitis and his platelet count was low and they from there started investigating what was going on. So, my first suggestion is make sure you get your health checkup otherwise he would not have known about this. His oncologist immediately sent him to UAB transplant center. He was, they said, an ideal candidate for the transplant. He was diagnosed with high risk. He is 63. He has went through all of the testing and multiple donors were found for him. He was supposed to have transplanted June 29, but right two weeks before he was to go in they did the pulmonary study and his… the only thing that did not pass on it was the FEV1. This is the amount of air that you exhale. So they were concerned because when you go into transplant you want your lungs to be at their best. He was a nonsmoker, but what they determined is that he has… did some CT scans, but the small capillaries and were restricted and I think he had asthma probably due to related allergies. So, they started him on a inhaler that has almost stopped the wheezing. He also was told to lose

weight. Between… He has prediabetes but that was one factor. He has afib which was another factor that put him at risk but the thing that sent him over the top was the overweight and the FEV1 failure. So, he has lost 25 pounds in the last three months. He really needs to lose 75, but he's going till he's going to lose 50. I think that will put him at a good level. He's already breathing better. The inhaler is working marvelously. I mean, he goes back to the pulmonary doctor September 3. He's even got to where he's walking in the mall. He just walks and stops and that's the big thing is the exercise. So, push yourself if you can get to a point. September 3 (inaudible) have much better results. So, I'm thinking he will maybe go into transplant in October or thereabout. I was an MDS seminar in, I think, it was February up at Vanderbilt and it was so informative. I thought well, I'm going to come back today because I can even learn more. The MDS Foundation is a wonderful support group. The one thing that she talked about was live your life and continue to live. Yes, he has… He's had to have two infusions and they started him on Vidaza also. His blasts dropped from 11 percent down to zero percent after the second Vidaza treatment. So, they're doing what they're… the supportive type thing. We had planned on taking a trip to Alaska at the end of May and just hated giving that cruise up. The doctors weren't with us and because of his fatigue level we ended up renting a scooter for him to use onboard. So, there are ways to continue your lifestyle with fatigue and other things and your doctors will work with you. So, that live is… find a way to do it. We are just as busy as we were before, but we just have learned to work around it.

Rebekah Barr: Make some modifications.

Q43: So, that's where we're at now.

Q44: Hi. My name is (Attendee) and my husband here is the reason I'm here because he takes such great care of me and I couldn't have made it through all this without him because I've had a lot of problems. Last year I had an aortic valve replacement and then I ended up in the hospital with a strange blood disease and spent a week there and it about killed me and they couldn't find out what was wrong with me and January we went to the Mayo Clinic and he said you have MDS and then the Emory doctor said, "Oh, no you don't." So, you don't really know what you do or don't have and you do get a second opinion and sometimes they conflict and so what do you do? I don't know. So, I have my blood doctor and I got to her and she's put me on Procrit and I stay tired a lot and I'd love to know what everybody here does to help build their blood back up. Is there a secret other than eating liver and I'd like to know what everybody else does as far as diet. I try to stay active and then I broke six bones in my foot and I couldn't walk. It's been one thing after another, but we're here, we're happy and we're still doing it. So, everybody, thank you all.

Q45: HI my name is (Attendee) and I'm from Little River, South Carolina and I was diagnosed almost two years ago and with MDS, low risk, like three percent and I go to the Coastal Cancer Center every week and I get a shot of Procrit, 60,000 units, and my hemoglobin is running roughly around 11. Some weeks it's 10.5, next week it's 11.6. Nothing is the same. Now, this has

been the third doctor that I've been to that tells me hang on, you're doing fine. Don't talk about transplants or anything like that and like you, I'm 67. So, there's a timetable here, I think, and yet they just keep telling me hang in there, you're doing good and like I said I go to the Cancer Center once a week. So, that kind of disrupts your schedule, but for traveling purposes, but hey you do what you can and yes, I try to eat liver once a week. (Laughing) as well as carrot juice, tomato juice, beet juice. My wife gives me all that. For platelets.

Q46: I'm his wife. I'm just around.

Q47: I want to thank the good doctor and you for your wonderful presentation first of all. The one thing I think more that I'd like to create more awareness for MDS. It seems to me that all of the publicity is with the Cancer Society and so I never hear anything about MDS and I guess maybe this is aimed more at… is Deborah still here? I guess she is somewhere. What can we do to create more awareness so that we could have more research to lick this thing? Thank you.

Q48: My name is (Attendee). About five years ago, my red blood cell counts fell below the normal ranges. I was diagnosed a little bit under two years ago with MDS after the bone marrow transplant. My hemoglobin dropped to about 7.7 after six rounds of Procrit. I stopped the Procrit about two months ago and my counts went back up. So, I'm not sure where we go from here. Looking at the doctors recommending Dacogen when my hemoglobin drops below seven. I'm nervous. I've read a fair amount about the side effects of the drug and I guess I'm trying still even though I was going to try it for two cycles, I'm looking supportive care that might fit my lifestyle a whole lot better. I'm not sure. So, it's been a great presentation. I really love the book that you guys put together. So, thank you.

Q49: Hi. My name is (Attendee). I am 73 and a year ago I was diagnosed with low grade, but the Intermediate 1 level and I was put on Vidaza and I feel good, I feel strong and the only thing that is bothering me is I just don't mess around bad colds. I got one over Christmas and just thought well, I'll get over it, but I really didn't and wounded up in the emergency room with a temperature of 101 and that came back down with some antibiotics, but other than that I don't have to get transfusions. I'm doing pretty well right now.

Rebekah Barr: Thank you, everyone. I think we're going to break for lunch and then after lunch we'll get back together and we'll let you guys share some of your experiences and help each other. Okay? Thank you.