



Speakers:

Richard Helmer, III, MD

Audrey Hassan: Welcome, everybody. Good morning. I think we're going to get started. Everybody's here. My name is Audrey Hassan. I'm the patient liaison with the MDS Foundation and Tracey Iraca, my colleague is here. I think many of you met... There's Tracey over there. Waive, Tracey. I want to say thank you to Baxalta, Celgene and Novartis for supporting our program today which will begin shortly. We are very fortunate to have Dr. Richard Helmer here from Texas Midtown Oncology and Jean Ridgway from the University of Chicago. She's a member of our Nurse Leadership Board. So, they've donated their time today. So thank you all for coming. Immediately following our program, we're going to have the bonus of Dr. Stuart Goldberg coming from New Jersey University of Hackensack and he'll be doing a talk on iron overload. So, we you can all stay for that. So, that'll be immediately following this program. It won't take much longer. We'll probably be over about two o'clock the same. So welcome and without further ado I'd like you to all join me welcoming Dr. Helmer.

(Applause)

Richard Helmer, III, MD: Okay. So, kind of an informal talk. If you want to jump in and ask a question, please feel free to do so. So, can you all see from...? Uh-oh. We're in trouble already. So, how do I advance? If we had a three year old here, it wouldn't be a problem. There we go. Okay.

So, the myelodysplastic syndromes by the World Health authority definition, it's a group of clonal stem cell disorders characterized by cytopenia which means a low count. So if a red cell count is supposed to be a hemoglobin of 12 and you have anemia, a hemoglobin of 10 that's a cytopenia. It's also characterized by dysplasia in one or more of the myeloid cell lines. Dysplasia means abnormal maturation when you look at it under the microscope. So, these are characterized by abnormal morphology and low numbers. It's characterized by ineffective hematopoiesis or production of red cells and an increased risk of aggression to acute leukemia.

Looking at the diagram of the cells, I'm sure many of you know this, but just to review there is a stem cell, multi potential stem cell that is in the bone marrow and when there's a bone marrow transplant or a peripheral blood stem cell collection, you're trying to get these multi potential stem cells that have under the right stimulus can mature down different cell lines. Lymphoid elements over here. Plasma cells, cancer of that is multiple myeloma. Over on the left side there's a common progenitor cell that can differentiate into megakaryocytes and these are the cells that make the platelets. Then the erythrocytes, red cells and then the white cells, the myeloblast and what we're interested in primarily are the neutrophils. These are the ones that fight infection. So, you have the megakaryocytes, platelets, red cells and the granulocytes and so just a picture of what we see when we do a bone marrow examination. On the left are more normal appearing red cell maturation. A large cell over a period of time takes on hemoglobin and

the color changes to more of a pink color and then as the red cells is extruded from the marrow it loses the nucleus and then you have the red cell which under normal conditions lasts about 120 days. On the right you see what we see in myelodysplasia in some cases. Abnormal maturation and you see here what we call popcorn nuclei or nuclear karaxis (sp? 4:59).

Ring sideroblasts. This is an iron stain and so what you're looking at is iron in the bone marrow, but you see these large blue accumulations around the nucleus and these are not in all conditions but ring sideroblasts are part of the system of MDS. The spliceosome gene, SF3B1 is seen in over 50 percent of patients with MDS, but not all of them will have ring sideroblast. The spliceosome, this is a little cartoon, is a... it's amazing what you can find on the Internet. The spliceosome is kind of an organelle within the cytoplasm that takes these messages from the nucleus and as I look at it kind of like it's a paragraph and these things come in and they edit out a lot of stuff and so you go from a paragraph edited down to a sentence and then that can then meet up with the other machinery and produce proteins and stuff like that, given additional genetic messages. There are about four spliceosomes or four different molecules and the SF3 has been recently described and there are some other ones and they sometimes will be indicative of response to therapy and this is stuff that's going to be coming along just... it's come along in the last few years and what we'll be dealing with probably in the next five to 10 years.

Granulocyte development. The myeloblast, everybody has myeloblast. When they accumulate then that's the trouble, but you can see the orderly maturation to what we call a polymorphing nuclear leukocyte which will be either two or three lobes, sometimes four. On this side you see the dysplastic elements. Oftentimes less granularity and the nucleus is not as distinct and as you see over on the left side and this is what when we're looking at a bone marrow, we're grading the development to give us an idea if there's these changes of dysplasia. This is a situation that you see not infrequently in MDS and it's a two lobed granulocyte and so when you're looking at the peripheral blood when somebody's referred for anemia or low white count and you're looking at the blood smear and you see that that's kind of a tipoff of what may be occurring.

Megakaryocytes are the large cells that made platelets. On the left you see the normal. They're hyper segmented and you see the granularity of the cytoplasm. On the right, you see a uni nuclear cell and you see small cells which we call micromegakaryocytes and that's also seen in MDS. Of course there have been several classifications over the years. This was the one that came out in 2008 and so when we read the bone marrow and we go through all that then a name comes up and so that's what is coded out on the bone marrow report. So, the refractory anemia with ring sideroblasts, deletion of the 5Q and I'll show you what that is. That's the long arm of the fifth chromosome and then these other definitions classifications and this is now changing to a new one that's going to be coming out this year that there was a conference, I believe, in Chicago last year that brought together Europeans and Americans and other people from around the country and it was, I think, sponsored by the Myelodysplasia Foundation and so this is a new coding system, classification system, that will bring in more information than the 2008. At this point though this is still primarily on morphology and the presence of cytopenias and with time

and now with the sequencing that is going on a lot of mutations are coming along and there are somewhere around 40 or 50 mutations in MDS that are seen quite frequently. They're not always associated with disease. They may be kind of bystanders, but there are more and more of these genetic events, somatic mutations that are now being picked up that will probably in the next few years begin to direct therapy.

So, that was the classification and so then there's a clinical system that we go by called the International Prognostic Scoring System and that came along about 10 or 15 years ago and then about two or three years ago it was revised to kind of bring in more information in how to talk to the patient as far as what you expect to see as far as the time involvement and kind of a predictor of what the prognosis is and then is... Actually, this is the chart and you don't have to sit down and write about it or you may have... I don't know if you have it in here or not, but if you go to the Myelodysplasia Foundation website they have this data in there and they also have the ability to calculate a score. So, this is at the top the prognostic score you look at cytogenetics and then here are the cytogenetics. So when we do the bone marrow, we send the cells off for analysis and we'll get back... after two or three weeks we'll get back a report and you can see that some have very good predictive value and some are very poor. Complex abnormalities, poor loss of number seven, intermediate Trisomy 8. So, we look at that and that helps us determine what the score value will be and then the percentage of bone marrow blast in the marrow. So, you sit there and we do 1,000 or 2,000 cell count differential and then you come up with a blast number and you just plug that in. The hemoglobin, if it's 10... eight to 10 or less than eight, platelets over 100,000 and 50 to 100 and then less than 50 and then the absolute neutrophil count and so these all are values that this gives you and then when you're sitting there with the patient you can plug those in and come up with a prognostic risk category to talk to them about what you expect to see and then this can affect how you go about treating. So and this also this is age related. It's calculated for a 70 year old person and I'll show you in a minute how you can change that. There's a formula for putting in someone that's 75 or someone that's 55, but then you get the risk score and so you're... either the very low, low, intermediate, high, or very high. Now the old one had only four. It had a Low Risk, Intermediate 1, Intermediate 2 and a High Risk. This has further defined it and it kind of gives you an idea of what the idea of what the future has in store. So if somebody comes in and they go through all this and they have a 1.5 or less, their survival, this is median survival. So, they're about 8.8 years median survival. So, you're going to take care of that person different. You're going to talk to them differently about somebody that comes in and they have a lot of blasts and they have abnormalities and they have a high score. You're looking at survival of less than a year and then the bottom line remember we talked about the progression to acute leukemia and so when you look at the very low this is progression 25 percent having acute leukemia and the very low group this was not reached. In the low group 10.8 years before you see 25 percent of those develop in acute leukemia and then for the very high less than a year. So, that helps in discussion with the patient what you're going to do and then how you may choose to... what therapy you choose.

The chromosome looks kind of like an X. Remember there's 46 chromosomes and two of them are the X and the Y. P is the short arm, Q is the long arm and so in the 5 deletion Q or 5delQ, you have deletion of the long arm and these people can be treated with a medicine called Revlimid and they have a good response with that. Again, the chromosome, the P, the Q and then in the middle is the central mirror where it holds together. Down here are the telomeres and there's actually now they're finding abnormalities that may affect treatment of MDS patients also with abnormalities in the telomere.

If I'm going too fast or you want to discuss it let me know. Again, the tables... Now, I said this was set up for people that are 70. That's the reference point. So if somebody comes in with refractory anemia, whatever and you go through the process and their score is a three, you can see that they're kind of right on the border for the low and their intermediate and so that's for a 70 year old. If somebody's 50, they're in the low, but if they're 85, you can see that they're in their intermediate. So, this is kind of age adjusted and there's actually a formula. You don't have to have the chart but there's a formula that you can plug in and get that information.

So, the goals of therapy. The patients oftentimes are transfusion dependent over a period of time. So, the goals of therapy are to decrease those requirements, to delay progression to acute leukemia, improvement in their quality of life and extend survival. That's really the bottom line. You want the treatment to be readily available, so you can get it not only in Austin and Chicago, but you can get it in Fort Wayne and Denver and wherever. You want it not to be excessive and we know a lot of the medications are extremely expensive that they're approved by insurance and as time goes on these treatments are going to become more targeted and that's based on the genetic analysis that's now going on, that's been going on and people are going back and plugging those values into some of the old studies to see if there are subgroups of patients that have a certain characteristic that respond better to a certain medication than others and then, of course, limited side effects.

Right now as far as approved therapy for MDS there're only three and there hasn't really been any great... there hasn't been any new medicines that have come online in the last 10 years and probably in the next year or two there probably won't be any. 5-Azacitidine is a medicine that's given once a month for seven days and it's a subcutaneous injection. Decitabine was approved about 10 – 11 years ago. It's given intravenously. It's given five days a week, one week out of every four and then Lenalidomide for the 5Q- is an oral medicine. They've also found that some of the patients that are not 5Q- that have ... in the low or very low group are responsive to Lenalidomide even though they're not 5Q- and so for some patients that's been a benefit for their anemia for treatment. Unfortunately, all of these patients not everybody responds to the 5-Aza or the Decitabine. These are what we call hypomethylating agents. At some point the genetic structure of the cell turns off different genes with these methyl groups and so 5-Aza and Decitabine come in and remove the methyl groups and allow for improvement in their counts. These people will respond to the therapy. Some do not everybody does. If they respond we usually tend to keep them on the medication for a long time, for as long as they can, but these

people will over a period of time relapse and so there's no actual cure at this point for MDS. The only cure is a hematopoietic stem cell transplant. The problem is that these people generally are older and have other comorbidities and so the process itself is not failsafe and people die during the transplant process. If you have a young patient or even a fit older patient that has a suitable donor then that would be something to consider up front. A lot of people will say at first I don't want to do that, but as time goes on and things start to change then many times they'll change their mind.

I have a friend now whose actually she's going to back to East. Her brother's taken care of in a center back there. He's in his 70s. She's in her 60s and she's getting ready to donate her stem cells for him. So, it's not something that you routinely do for older patients, but that really is the only thing that's curative.

Now that really, I think, is kind of... I think that's it as far as the overview. Does anybody have any questions on...? Yes, ma'am.

Q1: (inaudible 20:53)

Richard Helmer, III, MD: Procrit. Okay. So, Procrit or Aranesp which is the long acting form are frequently given just for the anemia. So if somebody comes in and they're in a low or very low or intermediate group and you get a feeling of what their overall situation is and if they're primarily anemic, I'll just start somebody on Procrit and it's given either weekly or the Aranesp can be given every three weeks, but it's a medicine called Erythropoietin. The kidney makes erythropoietin. It's a hormone that when the blood flows through the kidney if it senses that the patient is anemic then the kidney puts out erythropoietin and that stimulates the bone marrow to compensate and to make more red cells. In patients with MDS oftentimes you'll find a low erythropoietin level. If their level is less than 500 then they generally will respond to treatment with Procrit. Now, there's some other medications. Generally, we don't use granulocyte colony stimulating factor, Neupogen or Neulasta, because of the concern about progressing into leukemia and there are also medicines for the platelets, oral and IV, that you can give to stimulate platelet production, but those are generally in the patients that are in the low to very low to intermediate group. When they start getting in the high or higher then you're giving other medications.

Q1: (inaudible 22:46)

Richard Helmer, III, MD: Yeah. Now was that 2012, was that... what group as far as the risk group?

Q1: I really don't. I really don't. She was just sent there because she was anemic. They kept saying she was anemic. So, I was assuming it was the red blood cells that were the problem.

Richard Helmer, III, MD: Well, there are other reasons... I mean, people that can... Older people will have oftentimes a diminished renal function and so in the process of working somebody up you have to exclude all these other disorders and so if somebody's had recurrent urinary tract infections and chronic pyelonephritis and renal insufficiency from that they will respond... their anemia will respond to Procrit injections. So, you always have to do the other tests to exclude other conditions and then we have some ladies here that have the medication for platelets and these are all the platelet stimulating factors can be used in other conditions, too, but it's been used more in or it is being used more in MDS now. Sometimes people with Trisomy 8 will respond to immunosuppression and so cyclosporine has been given in some of those patients and respond.

Have you all heard about checkpoint inhibitors? I think you heard President Carter had melanoma and received a checkpoint inhibitor. So, what happens is that the tumor cell is when it's in the body it has different antigens and so it's recognized by these cells that sense out and detect these abnormal cells. They go then to the marrow, recruit T cells and then T cells, T lymphocytes come back and attack the cancer cell. Well, the cancer cell has then a mechanism kind of like a bumper that keeps the T cell away. So, these new medicines remove that bumper and so one of the medicines called Pembrolizumab is a checkpoint inhibitor that's been used in MDS and so there are studies going on with the use of that. People have tried combinations of the hypomethylating agents with Lenalidomide and with other medications really without any great success. So, it's kind of as far as the treatment in the last 10 – 15 years we really haven't had a lot come along. We're probably standing in front of a door that's going to open up and there's going to be new stuff, but it'll probably be targeted based on what the genetic markers will show when you do the examination. Does that make sense?

Q1: (Agreement sound)

Q2: (inaudible 26:10)

Richard Helmer, III, MD: What about the 5Q-? Well, it's not a real common one. I can't tell you what the percentage is, but the... in doing the evaluation and getting the chromosomes then you find out that it's a 5Q- or some subtle morphologically changes that you can sometimes pick up that would suggest that, but the treatment is Lenalidomide or what we call Revlimid and that's not without some side effects, too, as far as the blood count. So, you have to oftentimes start low and build up on the dose because it can cause the platelet count and the white count to fall, but if somebody comes in and they have a 5Q-, Lenalidomide is the treatment of choice.

Q3: (inaudible 27:18) is there something that typically is looked at as a last option after doing medications for a while that aren't working?

Richard Helmer, III, MD: I think it's based on the age. If somebody comes in and they're in their 50s or 40s or early 60s, that may move up to one of the first things that you want to do.

Now if that is... I mean, but it's also based on what the IPSS score is, too, because we're dealing with something that's not curable and the only cure is the stem cell transplant.

Q3: Can you have more than one of those if something falters with it?

Richard Helmer, III, MD: Well, in other conditions you do. I got several patients with myeloma that have had multiple stem cells transplants, but they're using their own blood and so when you have somebody with myeloma they come in and you treat them and you get the bone marrow pretty much cleansed of the cancer cells. Then you save... They're sent to the transplant center and they harvest the stem cells, save those and then give them intensive chemotherapy and then reinfuse their own cells, so they don't have a reaction, immune reaction, to the cells as being foreign and so then they repopulate the marrow with normal cells and then if they relapse then oftentimes you can go back and get some of the stem cells that were still being saved. With MDS, you're using somebody else's blood. I'm sure somebody's that I don't know as far as if they've been transfused more or if they've been treated more than once, but there's also an older population and it's not uncommon... When you got to pick out people that don't have a lot of comorbidities, heart disease, they have diabetes, kidney disease, stuff like that.

Q4: My question was my wife tried all of these and the only thing that's given her a positive response is the cyclosporine and so she's almost 19 months now transfusion free. My question is is what are the long term effects of long term use of cyclosporine?

Richard Helmer, III, MD: Well, it's more immune... I can't answer that for you. I think the question would be turned around what is the cost benefit ratio and I would think that with a condition that is not curable the prolongation with something like that is what you want to look at. As long as there're not severe side effects then it's primarily immune suppression. Does that make sense?

Q4: Sure.

Richard Helmer, III, MD: So, you see people that have been taking immune suppressant agents for decades that are either being getting it for arthritis or they've had a transplant for some other disorder and their own immune suppression. So, people that have kidney disease, with a kidney transplant or a heart transplant you see people on chronic suppressive therapy. So, there's always a risk of lymphoma developing in people that are on immune suppression. Cyclosporine, I'm not sure that's very high.

Q4: Thank you.

Q5: I have a few questions. Long term effects of Revlimid (inaudible 31:12) Is it true that it does cause secondary cancers and your thoughts on an identical twin being the donor.

Richard Helmer, III, MD: Well as far as Revlimid, we see it more in the use in patients with myeloma because that's where it really was... It's a derivative of Thalidomide. So, Thalidomide as you recall back in the '50s, I think it was, was given to pregnant women for nausea and for sleep and stuff like that and so you then had all these babies that had no arms and legs and so then that was banned for use and then beginning probably maybe around 20 – 25 years ago, Thalidomide then came back and was being used in the treatment of Myeloma and some other conditions and it had side effects from neuropathy, people would have a really bad tingling and stuff like that and so then Revlimid was a second generation and we've been using Revlimid now for, I think, well over 10 years in the treatment of myeloma and I don't know that I've seen any secondary malignancies related to that. I mean, you're dealing with a condition that's unstable in the first place and so it may be difficult to say was it due to the medication or it was the underlying bone marrow disease that led to the second malignancy and then it would be based on what type malignancy. If female then you have to be concerned about ovarian or breast cancer not necessarily related to the Revlimid and then your other question was about identical twin. I'm not a transplanter. I don't know, but I would think that that would probably be the optimum as far as a donor. Now, in an identical twin then you have the same genetic make-up and so you don't have as much of the rejection, immune related rejection process that you do if somebody is not an identical twin, but also there is a condition called the transplant or graft versus leukemic effect and so that can sometimes if somebody like it's a brother or a sister or somebody that's not related, but they have the same genetic make-up they're still going to see the body as foreign, the cells that have been transplanted and so when they see the leukemic cells then you also have the effect of the graft versus the leukemic effect, which is sometimes (inaudible 34:12) and so sometimes what they do is the immune medications may let up a little bit just so that there's an immune reaction fighting the leukemic cells, but as far as MDS I would think probably the best thing would be identical twin. Not very many people have identical twins.

Q5: We're lucky.

Richard Helmer, III, MD: Yeah and that's also a benefit, too, because if you have to get platelets for a platelet transfusions then she generally would not develop antibodies to platelets like if it was just a random donor. So, transfusions are one of the things that we deal with. Generally, the red cell transfusions are what we deal with most often. Platelets we try to avoid. Platelets only last a few hours and so the more platelets you give the more rapidly somebody becomes immunized proteins and so that in part the benefit of giving the platelet stimulating agents in order to raise the platelet count and as far as... so, there Procrit and then the two stimulating agents for platelets then there's the granulocyte colony stimulating, the GCSF or Neupogen. We try not to do that because it can... there's always a concern that it can push the blasts, increase the number of blasts, myeloblasts in a leukemic manner.

Q6: (inaudible 36:00) Can it engender a long term fevers of unknown origin like eight months and nondiagnosable. I just was curious if it effected white cells that much.

Richard Helmer, III, MD: Did you all hear the question about fever? You see that generally you don't see that in MDS patients as far as the FUO, the fever of unknown origin, but you can have acute (inaudible 36:33) illnesses and it's not oftentimes it's related to therapy but also you're working with a situation where the white count may be low in the first place and so you come along and get therapy and you further delay or further enhance the low white count and so sore throat, urinary tract infections, bronchitis are things we have to look for. And so a lot of these people are smokers, too, or have been and so they may have chronic bronchitis and so as we... my chief always said that as we got older, everything started to get rotten, your teeth, the gut, the prostate, things like that. So, there's source of infection and then as the white count falls then one is more prone for infection.

Q6: Thank you.

Richard Helmer, III, MD: So, the sad thing is in the last 10 – 15 years we haven't had any new medications that have come along, but we're probably just standing on the lip of the cup of things that's going to be occurring... that will be occurring in the next five – 10 years based on the genetic analysis that almost always tumors are going through and so there are large studies that will be underway and that really kind of is the plea if for some reason it looks like things are changing and there needs to be different therapy, they're always we need to look for experimental regimens and referral to centers that may have study programs that we might be able to learn from. That's not always easy because you're dealing with older patients and so somebody may not want to be able... can't drive Houston or can't drive to San Antonio so you want to have, if we can, research advantages in the local community and that's not always the case. MDS has tried to support that and... or the Myelodysplasia Foundation has tried to support that as far as getting research programs to the local level. So, right now it's not, like I said, a curable process unless you have the stem cell transplant, but hopefully with the new medications that may become more of chronic illness.

That's it? Any other questions? Well, I hope I kind of gave you an overview of what the bone marrow looks like, the peripheral blood and what the treatment options have been and hopefully what's going to happen in the near future.

(Applause)