Speakers:
Amit Verma, MD
Aditi Shastri, MD
Ira Braunschweig, MD
Arun Sunny, PA

Audrey Hassan: Great. That would be great. The bathrooms are right here, right next door. Please also feel free. It's very informal, so please if you want more food get up, help yourself. We want you all to be comfortable tonight.

So, without further ado I'd like to introduce our guest speakers. We are honored and we're very happy that they donated their time tonight to participate in this forum. We have Dr. Amit Verma, Dr. Aditi Shastri, Ira Braunschweig and Arun Sunny. Without further ado I'd like to get the program started and if you please join me in welcoming Dr. Verma that would be wonderful. Thank you.

(Applause)

Amit Verma, MD: Audrey. It's a big pleasure for me to be here. I always (inaudible 0:58) that it's far greater pleasure to talk to patients and families rather than giving presentations to our scientific colleagues because you hear feedback directly relevant that directly affects people and this is the first time we're doing this. So, we are a little bit unfamiliar with these patient forums that the MDS Foundation organizes, but we want to make it as informal as possible. So, please interrupt us at any point if you have any questions and we want to make it interactive and the only purpose of this to help you guys navigate (inaudible 1:43 – 1:59). Thank you. So, Audrey told us that maybe we should give short presentations. That way we could show you some data about MDS, what we are doing here in Montefiore with regards to MDS and that might also be a stimulus for you guys to interrupt us and ask us questions.

So, I wanted to start off by showing you some… we don't have a pointer here so I'll just walk you through the slides myself. So, I wanted to start this off by a little introduction on what this disease is, MDS. I'm sure a lot of you already know a lot of things that I'm going to talk about and I wanted to keep it simple, but still concentrate on the main things that we focus on as hematologists So, MDS, it's a short form of a big name, Myelodysplastic Syndromes, and the name comes from two words. Myelo which means blood and dysplastic means something that's not alright. You know something that's altered, dysplasia, and this disease is really a group of bunch of blood disorders and the unifying themes for all of these disease that are grouped under MDS is that the bone marrow where all the cells are bing made doesn't function properly. So, there's a bone marrow malfunction and the net result is that the bone marrow doesn't make enough cells properly. So, you have low red cells, white cells or platelets or all of them and you get symptoms, you get problems that you feel. The reason we call it dysplasia is when we take some of your patients you've had this bone marrow procedure where we take a little sample from

the bone marrow, put it on a slide and look at it under a microscope. What we find is that the cells don't look normal. They look dysplastic. So, that's why we call this disease myelodysplasia and the third thing that defines this disease is that there are some MDS patients that can progress to leukemia to type of leukemia called acute myeloid leukemia or AML.

Now, if you look at the overall numbers in the US when I started doing MDS about 10 – 11 years ago there wasn't much activity going on in this disease. I would say there would be seven or eight researchers working in MDS in the US and there wasn't a single drug approved for MDS, but in the last five years there's been tremendous excitement and activity in this field and that is also reflected in how many numbers of MDS patients we are now diagnosing. So, if you look at the official numbers as I put in the slide official numbers is 10,000 new cases every year in the US, but the real true number is close to 50,000 and they get at this number by just looking at insurance claims which is more accurate than these epidemiological studies and when you look at all the patients that get diagnosed with MDS it tends to occur as we age. So, the median age is 70 years and I'll show you a slide how the incidence… how the frequency of MDS goes up as we age.

So, what's really going on in this disease? So, this diagram shows you that the bone marrow is where all the blood is being made is all our bones are hollow. So, all our bones have marrow inside them and that's where you find these stem cells that give rise to white cells, many different kinds of white cells. They give rise to platelets these small cells that help clot the blood and then they give rise to red cells and this cartoon shows you a very simplified version of the same thing. So, you hae a stem cell that has the capacity to give rise to all of these cells and this process via which a stem cell becomes a mature cell is called hematopoiesis. Big word, but this process is kind of complex. It's very complicated. Many different steps, many different things that regulated and there are factors that make the stem cells make more an more cells and then there are factors, substances, proteins, in the blood that can stop the stem cell from making more blood because you don't want it to go unchecked. If the cell division goes unchecked you can end up with leukemia. So, there's always a balance between expositive and the negative. In MDS what we find is that this balance is lost. So, the negative factors may become more. So, there is defective maturation of stem cells to mature cells and you end up with low blood counts and this makes us researchers think of how can we reverse this negative influence, how can we restore the balance and when we talk about some of the treatments for this disease you'll appreciate this point more.

So, this is sort of a simplified diagram of what really happens in MDS. So, our thinking is that this is a disease that takes many, many years and decades to develop and at some point there is a mutation, a gene mutation or a chromosomal change that occurs in stem cells in the bone marrow and this may affect very few cells when it first happens. Gradually over the course of time these abnormal stem cells as depicted by the pink color start growing and they interact with the other cells in our body – immune cells, surrounding cells, and they create this inflammation in the bone marrow that ends up killing a lot of normal healthy stem cells. So, over the course of time

the healthy stem cells go down and the unhealthy MDS stem cells go up and you up end with low blood counts. That's what we call as low risk disease with most of patients with MDS actually have low risk disease.

So, what I'm trying to say is that there are millions and millions of these stem cells that live in the bone marrow. Let's say according to due to some environmental exposure or something that we don't know of one of these cells acquires a bad mutation. So, instead of being a normal stem cell it becomes a sort of MDS stem cell. Over the course of time this abnormal cell will grow, but the normal will shrink and then when it sort of takes over the whole bone marrow the blood counts will fall and then you present with this disease, but this process takes decades to happen. It's a slow process. That's partly the reason why we think this disease presents when the age is more than 60, more than 65. Sometimes these abnormal cells can undergo more changes. You can get more mutations, you can get more genetic changes and then it can switch to a high risk MDS or leukemia. So, MDS can be low risk where the main problem is low blood counts or it can be high risk where it's more like a leukemia and we are worried about preventing the transformation from MDS to leukemia and the reason it's important to understand low risk and high risk is the treatment strategy is different. Dr. Shastri will briefly tell you about treatment and we treat low risk slightly differently than how we treat high risk MDS.

This graph shows you how the numbers change as we age. So, these are rates of MDS seen per 100,000 population in the US and as you can see the rate of MDS really goes up after the age of 65.

So, you go to a… so what happens with most people is they experience some sort of symptom which makes them go to the doctor and the symptoms usually are related to low blood counts. So, if you have low numbers of red cells you have anemia and the most common symptom for MDS is fatigue. If you have low numbers of white cells your capacity to fight infections is reduced and you can have more severe infections or repeated infections. If you have low platelets then you are more likely to develop bruises, you're more likely to bleed. Brushing your teeth you may notice blood staining your gums or just a little bit of a knock might lead to a bruise. So, these are usually the three main types of symptoms people present with. Patients usually go to their doctor who does a blood count, notices that the blood counts are low. They try and see if there are any obvious causes for this, but when they can't find them they refer you to a hematologist and what we do is we look at your blood under a microscope. We usually end up doing a bone marrow test, bone marrow aspiration, and then looking at it under a microscope but more importantly we send those cells for genetic and cytogenetic testing and that as I'll tell you a little bit later on can allow us to determine how high the risk is for your disease.

So, what are these chromosomal changes that I've been mentioning? So, all of our genetic material in cells is organized in some of these chromosomes and what we see in MDS is that parts of certain chromosomes are missing. So, you have deletions in certain chromosomes and I put the common ones here, chromosome number five, chromosome number seven, chromosome

number 20. These are usually have parts of them missing in MDS and we use this to diagnose this disease when we do the bone marrow. In addition to these chromosomal deletions we also have gene mutations. So, I put some of these names. There's a whole long list of complicated names, but sometimes when you talk to a hematologist he might mention this gene P53 or a gene ID edge. These are actual genes that can get mutations when you have MDS and AML and now from a practical point in the last couple of years we can easily test for these mutations with just a sample of your peripheral blood. We don't need to do bone marrows. In the olden days we need to do bone marrows for everything and this is reimbursed by your insurance and we use these to do two things. One is to predict risk. Like if you have a P53 mutation your risk is slightly higher, but more importantly there are drugs that are coming out that can target these mutations. So, there is a mutation in a gene called ID edge. If you have a mutation in ID edge we actually have one approved drug that was approved last month and if you have a mutation in this gene FLT3 we have another drug that was approved this year. So, we have two drugs that were approved for these exact mutations and I think more are in the pipeline. More are coming.

Q1: (inaudible 15:14)

Amit Verma, MD: The drug blocks the cells that have this mutation. These mutations usually cause some activation of bad (inaudible 15:27) and the drug blocks them.

This slide I just put there to show you that hematologists can think in very complicated manner. We made these very complex classifications of MDS and every few years a bunch of hematologists get in a room and decide that the old one isn't good and we try and change it. So, if you can see there are many different versions that have undergone changes and the old one that we had that a lot of us still follow was this French-American-British classification and I don't want you to remember these names. What I want to tell you is that when you talk to your hematologist he'll frequently talk about these cells called blast cells. So, these blast cells are cells that are leukemia-like cells and when your hematologist does a bone marrow they count how many blast cells do you have in your bone marrow and the reason they do that is if you have less than five percent it's considered to be low risk. It's considered to be close to normal. If you have more than 20 percent of these blast cells in the marrow then we call it a leukemia and between five and 20 we call it high risk MDS. So, it's important to know what your hematologist is talking about when they talk of these blast cells.

So, the reason we do this, the reason we group them into these complex subtypes is because each of these subtypes has a different behavior in the clinic. As you can see these are these curves which are called survival curves. So, the light blue line which is the topmost line this is a disease is called MDS type called RARS, long name, refractory anemia with ring sideroblasts. Bottom line is this is a very low risk type of MDS that doesn't usually progress to acute leukemia. On the other hand the lowermost dotted line is this condition called RAB which is slightly more high risk and transforms more to leukemia, has more of an inclination to do that.

So, why do we do this? Now, the other thing your hematologist sometimes will tell you is this complicated scoring system called IPSS. It is short form for International Prognosis Scoring System. What this means is we look at three things in a patient. We look at the number of bone marrow blast cells that I just mentioned. We look at how many chromosomes in the test are altered and what chromosomes are affected and some are good, some are bad risk and some are we don't what they are so we call them intermediate and then the number of cytopenias means do you have just anemia or do you have anemia and low platelets or do you have anemia and low white count. So, we give a score for each and then we add up the score and we divide the risk into a low, intermediate or high and then we use that for treatment as Dr. Shastri will tell you and this is just a list of bunch of chromosomes that can be affected in MDS and as you can see 50 percent of MDS patients actually we cannot detect any chromosome changes at all. So, the reading comes back as normal, but now we have gene mutations and a lot of them turn out to have gene mutations that we can diagnose.

So, since this was I'm talking of chromosomes I just wanted to mention there is a sort of special type of MDS called 5Q MDS. This is an MDS in patients who have deletion of one arm of chromosome number five. So, this type of MDS is important to diagnose because patients who have this 5Q deletion respond very well to this drug called Revlimid which you'll hear about in a few minutes. This type of MDS is actually affects ladies more and other interesting thing in this MDS is platelet counts are actually increased as opposed to other MDSs their platelet counts are low. There is a nice response to Revlimid. You'll see the data and the chances of it transforming to leukemia are very low in this. It's actually less than 10 percent now after Revlimid has introduced.

So, this is a short introduction to MDS. It's getting more common now. I think more and more people are being diagnosed. These are some of the prominent people that have been in the news the last couple of years. Steve Walsh, the 49er's coach. Robin Roberts. I think a lot of us know she had breast cancer, got chemotherapy and then chemotherapy exposure caused changes in her bone marrow stem cells which led to MDS. So, I want to end here. This was meant to be an introduction and if you guys have any questions.

(Applause)

Amit Verma, MD: Okay. So and if you think of a question you can interrupt us at any point. So, Aditi is one of our colleagues in Montefiore and she's going to (inaudible 21:31)

Audrey Hassan: Can I just remind everyone to speak into the microphone and you have to depress, I think (inaudible 21:41). To the right. I'm sorry. (inaudible 21:46) to be heard. (inaudible 21:49) and when it's lit (inaudible). So, if you have a question if you could just press the button down while you're speaking that would be great.

Q2: (inaudible 22:14) the name of this guy who… I just missed the name of the man who you show with Nora Ephraim and Robin Roberts.

Amit Verma, MD: The (inaudible 22:24) 49ers.

Q2: Oh. Okay. Thanks.

Aditi Shastri, MD: Okay. Hello. Can everybody hear me okay? Alright. Hi. So, I just want to extend a warm welcome to everybody who's here today and for those of you that are not from the Bronx, so welcome to the Bronx and we're with the Montefiore Medical Center which is the biggest…

(END OF AUDIO)