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Speakers:

Amit Verma, MD

Aditi Shastri, MD

Ira Braunschweig, MD

Arun Sunny, PA

**Amit Verma, MD:** There are looking promising in MDS and you had asked this great question. How do we know what's going on in the clinical trial world, what the options are? So, the way I think the US system works is there are certain big centers that see a lot of MDS patients and these centers also have a few more clinical trial options to offer to patients and as was pointed out by my colleagues it's very important to have a nice discussion, exhaustive discussion with your family members, your loved ones as well as your hematologist on what the pros and cons of a particular clinical trial will be and I thought I could show you some examples of clinical trials that we have so if you hear about these drugs you can... here it is. So, you have a little background information and I think some of these drugs may actually be hopefully future and from a clinical trial experimental (inaudible 1:36 – 1:40). So here at Montefiore we are part of the Albert Einstein College of Medicine and we have two major hospitals in two parts of the Bronx and we have dedicated clinic where we see MDS patients. We are thankful to the support of the MDS Foundation who sends us patient referrals as well as provides informational booklets and other sources of help for our patients and the Leukemia and Lymphoma Society.

So, one trial that we have a clinical trial is with this drug called Eltrombopag. So, what is this Eltrombopag? It's a small chemical and it's a chemical drug. It's an oral pill that can increase platelet count in MDS patients and this complicated figure shows that this drug can bind to the receptor. This is the surface of a cell. This is a receptor. The drug is getting stuck here and it stimulates this pathway that leads to increased platelet production and the reason this is important is because as we all know low platelets can be a major problem in MDS and they're kind of hard to raise even with approved medicines, Revlimid, Azacitidine, Decitabine, platelets are particularly tough to raise and we can give platelet transfusions, but the effects of platelet transfusions are usually temporary. They don't last for too many days. So, this drug is approved by the FDA for treatment of a low platelet condition called ITP which is not MDS. It's an immune system problem that causes low platelets. The drug is approved and here in Montefiore a lot of research went into showing that this drug can not only increase platelets but in some cases also reduce the amounts of leukemic cells in certain patients and we also showed that this can be given in combination with Revlimid. You know, Revlimid is a good drug for some types of MDS, but the one big problem with Revlimid is it can actually decrease your platelets more. So, we showed in the lab that you can combine a platelet drug with Revlimid and you can have beneficial effects. So, we (inaudible 4:36) a clinical trial phase two means that all patients who go in this trial get this Eltrombopag drug in combination with Lenalidomide which is Revlimid and we purposely... you know, the one thing that clinical trials as some of you may have experienced they are very restrictive sometimes. They have very rigid criteria that you need to have kidney function like this or liver function like this. Only then you can enter it. So, because

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we were writing this trial we purposely made it very inclusive. We kept the restrictions to a minimum and we have been treating patients with low and intermediate risk MDS who have low platelets with this drug. We have treated 27 patients so far out of 15 have been treated for a sufficient period of time and 55 to 60 percent of them have responded very nicely not only increasing the platelets, but a lot of them have achieved increases in red cells and I just show you example of one of our patients who came to us with very low hemoglobin and very low platelets and if you see records in the clinic computer. For example, this is hemoglobin goes down, patients gets a transfusion, goes up then goes down again, transfusion. So, you see these mountain spikes and the same thing was happening with platelets. We started the medicine here. It took a little time, but gradually the platelets went up and the hemoglobin went up. I saw this patient today had a platelet count was about 100(inaudible 6:28). So, it's a big success story. It doesn't work in everybody, but we've had some decent successes with this.

Another trial we have I showed you this cartoon that stem cells give rise to red cells, white cells and platelets and you have positive proteins that stimulate this pathway and then you have negative proteins that kill this pathway and one of the negative proteins is this protein called TGF beta. It is very high in MDS and it prevents cells from maturing and if you can stop this drug from this protein from acting you can reverse the duration. So, you can increase blood counts. So, based on this (inaudible 7:21) we have a clinical trial with another oral drug that is blocking this protein called TGF beta.

**Q1:** Can you (inaudible 7:31).

**Amit Verma, MD:** Absolutely. So, you have stem cells that sit in the bone marrow and then gradually they become red cells. They have the capacity to generate white cells and platelets and this whole process is pushed in the right direction by positive factors like EPO, like GCSF and other proteins in the bone marrow, but then there are a bunch of negative signals that block this and one of the negative signals is this protein called TGF, transforming growth factor, and in MDS the levels of this are high. So, it's blocking your stem cells from making good numbers of red cells and white cells. So, what we are trying to do is let's say we blocked this. Can we increase blood counts and make you transfusion independent? That's the goal of this trial. So, there's a lot of data that we generate in the lab and now we have taken it to the clinic and we're trying to test it.

Okay. So, Dr. Shastri spent time in the lab and she looked at another protein which is called STAG3 and this protein is also very high in MDS and what you see here Dr. Braunschweig showed you the survival curves. These are MDS patients that had high levels of STAG3, didn't do so well and these are the patients who had low levels of STAG3 did a little better. So, the question is we know STAG3 is high in MDS and if you have high STAG3 you do worse. How can we make these guys do as good as them? The obvious answer is to block this STAG3 protein and Dr. Shastri has shown that there is an oral drug called Pyrimethamine which is a drug which has been there for 50 years. It's actually used to kill certain bacteria and certain fungi and what

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she found in the lab was that Pyrimethamine can actually block this harmful STAG3 protein also. So, it's a very safe drug, it's a very cheap drug and we are going to... we are testing it now in patients with intermediate-high risk MDS and we will see if this drug works as expected as it worked in the lab.

So, the important issue in MDS that Dr. Braunschweig mentioned and Dr. Shastri mentioned is you get this drug Azacitidine or you get this drug Decitabine. What happens once you don't respond to it or if you respond to it but after a few months you stop responding to it? So, this is a very important clinical issue in treatment of MDS and the FDA actually, the government also knows this and has been pushing pharmaceutical companies, biotech companies to develop new trial concepts and new medicines specifically for MDS patients that have failed Azacitidine. So, we have three trials open in our institution. One of them is this very interesting agent. It's actually a chemical. It's a peptide. It's small piece of protein. It's called ALRN. It's small company based out of Cambridge, Boston that makes this drug and this drug it's a complicated figure. Basically what it does is it activates this protein called p53 and then this protein when it's activated kills your bad stem cells, kills the bad MDS cells and that's been our hypothesis. We are treating patients actively on this trial and we are treating MDS patients that have specifically either failed Azacitidine or Decitabine or are relapsing after these agents. So, this is the peptide. This blue ring. It blocks the proteins that kill p53. This drug (inaudible 12:21) p53.

What else do we have? So, we also have another clinical trial with and new drug from this company GlaxoSmithKline. It's called LSD1 inhibitor. It has shown a lot of promise in acute leukemia and now they're testing it in MDS and we are giving it in combination with retinoic acid which is basically a vitamin, vitamin A which has shown to be very effective in certain types of acute leukemia and now what we are trying is combining this retinoic acid with this LSD1 inhibitor which is an oral drug and there are three sites in the US, we, Cornell and MD Anderson that are using this trial right now.

And lastly we have a trial which is a trial which uses this drug called PD1 antibody. Now, in the last five or 10 years, I would say, the big revolution in the field of oncology, not so much in blood cancers, but in solid tumors is the fact that we have these PD1 drugs that can stimulate your own immune system to fight your cancer. It is probably the biggest advance in the field of these solid tumors in the last, I would say, 20 – 30 years. Unfortunately, these PD1 antibodies have not been that successful in blood cancers, but there's a lot of emerging data from various labs around the country that when patients are on these Azacitidine and Decitabine drugs these PD1 antibodies may actually work better and the concept is you stimulate your own immune system to fight the leukemic cells. So, we have also participated in this trial and we have had some good success stories which I can tell you later with this combination. It's a pretty lightweight drug. This PD1 antibody doesn't really cause too many side effects and basically you continue on your Azacitidine but just get this additional injection on top of that.

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So, this is just some of the clinical trials that we have. As Dr. Braunschweig was mentioning it's important for MDS patients to know their risks, to know what options there are and there's no harm in taking second opinions. We tell it to all our patients. If you have any doubts we welcome you to talk to other people and our goal of our whole team is to make you guys feel better. We don't care if it's here or somewhere else.

So, I think after this we want to end with something more holistic. Arun is our physician assistant who specifically works with our MDS clinic and MDS patients and he's going to talk about some quality of life strategies.

**Q2:** Can I ask a question?

**Amit Verma, MD:** Yeah. Sure.

**Q2:** Are these trials (inaudible 15:53) pertaining to (inaudible).

**Amit Verma, MD:** So, it's a good question. So, some of them are and some of them are not. So, for example in this trial even patients who have not been exposed to Azacitidine can be enrolled.

**Q2:** (inaudible 16:11)

**Amit Verma, MD:** The top ones only for patients that have failed Azacitidine.

**Q2:** (inaudible 16:17 – 16:24)

**Amit Verma, MD:** Yes.

**Q2:** I have no idea what it is. Valproic acid.

**Amit Verma, MD:** So, valproic acid was in a way somewhat similar. It was an older generation, but this one is much, much more specific, more advanced, but you're... In a way these therapies are called epigenetic that they don't... They act on the DNA. So, in a way it's similar to valproic acid, but it's a pretty newer compound. It's a very different class of molecule.

**Q2:** The reason I ask because they did do a study in Germany. In fact, they're using it as a treatment there years ago I think valproic acid and (inaudible 17:13).

**Amit Verma, MD:** Yes. So, we did I would say eight or nine years ago we treated patients with Azacitidine and valproic acid combinations and we did an early study where everybody got this combination and the results look pretty good. We were getting responses that were quite high. Unfortunately, when they tested it in a bigger trial where... so, late phase trials they basically... the computer gives you the choice that patient A will be treated with a combination and patient B

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will be treated just with Azacitidine and at the end of the trial... So, you do this phase three trial where you will either get Azacitidine or you will get Azacitidine plus valproic acid and when we did this trial the valproic acid did not increase the chances of success.

**Q2:** But you aren't doing valproic acid and retinoid (inaudible 18:15)

**Amit Verma, MD:** No, we didn't do retinoid.

**Q2:** Thank you so very (inaudible 18:21)

**Amit Verma, MD:** Sure. Sure.

**Q3:** This is kind of a question (inaudible 18:26) diagnosed with MDS and you live in New York City or the area and you're looking for a place to have your care. I think it's... I mean, MDS Foundation informational website is extremely helpful because they focus on what they call Centers of Excellence and I can't imagine living in New York and having any kind of a disease or condition and not looking for someplace like that. So, my question really is we have options.

**Amit Verma, MD:** Yes.

**Q3:** Not just one place. We have options.

**Amit Verma, MD:** Absolutely.

**Q3:** And how no matter how you came to the diagnosis it may not have been through a person working at a Center for Excellence and you might feel actually we do that the services that are offered are more limited. There's not a single practitioner and you don't have a (inaudible 19:21) so that's... My question really has to do with once you've chosen where you want to go, the clinical trials, what if some that that you are eligible for is being studied somewhere else and you sort of touched on that and you see that there's Cornell and Montefiore together on this one.

**Amit Verma, MD:** Yes.

**Q3:** So, that's what my question is what is the...

**Amit Verma, MD:** How do you navigate this? Yeah.

**Q3:** And how you guys share your information.

**Amit Verma, MD:** Yes. Yes. So, I think the MDS community, the hematologists that deal with MDS, it's not a huge community and we all work well with each other. We are thankful to the MDS Foundation for creating this Center of Excellence network which really helps patients

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because you're hit with this diagnosis. You don't know what this big term means. It's, I think, very helpful you go to a center even if it's for just one visit or second opinion where it's been studied very thoroughly, but right... not every place has the same trials and you may be seeing a hematologist who doesn't have the perfect trial that you may want to enroll in. So, I can tell you from our personal experience we always encourage people to look and if we cannot give them the best possible trial option we have colleagues that we call all the time. A lot of times the reasons could be geographic. There are patients don't want to... (Inaudible 20:56) or insurance issues. There are a lot of other factors that play here, but us, our endeavor, is to try and get as many exciting new drugs that we hear of. So, I can give you our example. We're in the Bronx. It's a pretty populated place and we have a lot of patients live locally who come to us and then the best possible options that they can get in Sloan or MD Anderson, for example, and for most part we do, but if we don't we tell them to... we call our colleagues and we tell them to (inaudible 21:34). Yeah. Absolutely. So, we are very open (inaudible 21:38) because like Ira said we don't have a crystal... perfect crystal ball and we don't know in the end what will be the magic bullet for each patient. So, you have to be open.

**Q4:** (inaudible 21:58) and the patient is also recognized (inaudible).

**Amit Verma, MD:** Absolutely. So, if you're on a clinical trial a lot of times patients are seen in the community setting in private practice and they try FDA approved medicines, Revlimid, Azacitidine, and unfortunately if the patient does not get a good response then they send them to us and there are some trials where we can treat patients, but we don't need to see them on a weekly basis. We just see them maybe once a month sometimes even less than that and they are followed up with their local physician. We have patients that come from Jersey for this Eltrombopag drug and we see them maybe... in the first phase maybe once a month, but then we have connections with their local hematologist. All we need to see is their blood counts so they can fax it to us.

**Q5:** When you talk about (inaudible 22:59) you talk about clinical trials is there such a thing that is part of this (inaudible 23:07) so as a result...

**Amit Verma, MD:** Yes.

**Q5:** She and I are both coming to you and we think that we're both getting the same thing and we're (inaudible 23:14) getting nothing and...

**Amit Verma, MD:** So, the phase three trials where you have two different treatments are usually blinded where even I don't know what you're getting. Our pharmacists may not know so and then once they complete the trial then they call it unblinding and then you find out what you got. Usually, the government does not allow even in a phase three trial that one arm is going to be ineffective. Both arms have to be effective. You have to compare experimental therapy with a standard therapy otherwise nobody will give you permission to do it. So, there are safeguards.

**Q5:** By the FDA.

**Amit Verma, MD:** Yeah. It's not like you're just getting water.

**Q5:** (inaudible 23:59) like a mouse.

**Amit Verma, MD:** You know that is the most frequent question because patients come and they don't want... they say I don't want to be a guinea pig. I don't want to be an experiment and believe me our endeavor is to get these exciting new options for patients who have failed standard treatments, but we also are very cognizant of the fact that we cannot give something that's completely unproven. It has to be... it has to move through rigorous lab testing, animal testing and it has to show some glimmer of hope otherwise we will never do it.

Okay. So, Arun.

**Arun Sunny, PA:** And I want to thank Dr. Verma, Dr. Shastri and Dr. Braunschweig for this opportunity.

I'm here to talk about quality of life for people with MDS. Quality of life for people with MDS. So, this is a little outline. What do you know about symptoms and quality of life for MDS patients? What works to reduce fatigue? What causes distress in MDS patients, and what are the coping strategies.

So, I just want to ask you guys what are the main symptoms if someone is diagnosed with MDS that you know?

**Q6:** (inaudible 26:01)

**Arun Sunny, PA:** What are some of the main symptoms if someone has MDS that you know? What are the main symptoms that you're looking (inaudible 26:05)?

Oh, can't hear me? Oh, sorry. Okay. So, I just want to ask you guys what are the main symptoms that if someone has MDS that what were the main symptoms that we look at for if someone has MDS?

**Q7:** Fatigue.

**Arun Sunny, PA:** Okay. That's one thing. That's actually the main thing. That's the main symptom you look out for. Fatigue. So, Dr... Every doctor told you about MDS. It's a bone marrow disorder. It's a bone marrow disorder. Your bone marrow cannot produce enough stem cells that could proliferate and become like a red blood cell, white blood cell and platelets. So,

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people with MDS they're usually anemic. Anemia is a main symptom that people... that people have and every organ system in our body it needs... it needs red blood cells. Every organ system in our body needs blood and if you don't have red blood cells you will (inaudible 27:24) it will manifest itself as anemia and fatigue. So, those are the main symptom... that's the main symptom you could look out for, fatigue.

The next thing... so, how do you treat fatigue? How do you treat fatigue? So, another thing I want to tell you about fatigue. So, how do we quantify fatigue in someone with MDS? I want to ask you that. How do we quantify fatigue with someone with MDS? How do you look at for fatigue? Can someone tell me? How do you look out for for fatigue? Quantify fatigue in MDS? So, I mean, the main thing we look out for is the hemoglobin count. Hemoglobin count. That's the main thing we look out for. So, we have a lot of patients in our clinic with Dr. Verma. How do we quantify fatigue? So, we do for someone with MDS a blood count is very important, a blood count. So, we do frequent blood counts and we look out what we call a hemoglobin count or hemoglobin and the less than eight we usually give them transfusions. That's how we treat fatigue. We give them blood transfusions. That's how we treat fatigue and... but see a hemoglobin of eight, it's very... fatigue is very unique for a different patient. Fatigue is very unique for different patients. So, someone has let's say you have two patients, one has a hemoglobin of eight (inaudible 29:28) have a hemoglobin of eight and one have a hemoglobin of (inaudible 29:33 – 29:59). So, someone has a hemoglobin of eight and there's another patient who has the same hemoglobin of eight. So, see fatigue... how do we know who require more transfusion? So, we really have to look... we really have to listen to the patient and we really have to look for the symptoms and the main symptoms we look out for are shortness of breath. That's the main thing we look out for. Shortness of breath and some people palpitations, but there's another manifestation of anemia. So, how do we know one patient require two units of blood versus one unit of blood? So, the main... the patient will actually tell you. If you really listen carefully for the patient they will actually tell you and a good physical exam that's where a good physical exam come into play. So, these are the main symptoms for someone with MDS, fatigue, bruising, bleeding, bone pain, fever, skin rash mainly like (inaudible 31:22) if their platelets are low they have like what we call pinpoint bleeding, weight loss and stuff like that.

So, why do people get weight loss in some of the MDS? Do you know someone can tell me? Someone why do people get weight loss in people with MDS? Dr. Verma, can you tell me why people get... Yeah. So, what happens mainly is the loss of appetite. So, what happens is for some people with MDS their bone marrow is not working proper. Bone marrow is not working proper so some of these other organs like liver and spleen it could take over the bone marrow function and they could get enlarged like the spleen could get enlarged and the liver could get enlarged and what happens is some people when they take a little bit amount of food, the spleen could press on the belly and that could manifest as loss of appetite. So, that's a reason why some of these people they'll lose their appetite and they cannot eat a lot of food. That's why they manifest as weight loss and other reasons why. So, what we do we usually recommend people eating smaller meals at frequent times like every three to four hours we have them (inaudible



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32:54). So, there's another reason why people lose appetite. So, Dr. Verma all the doctors told you people with high risk MDS they're on what we call Vidaza, infusion Vidaza and Decitabine and stuff like that. They do go through what we call a recovery period. They do go through a recovery period. So, the way Vidaza and Decitabine works they have... the first year of treatment, the first year of treatment the blood counts are high, blood counts are high. So, there is a (inaudible 33:39) point about two weeks from the first day of treatment the blood counts will be low and then they'll recover. During that time, too, people... it'll be a side effect of the Vidaza people do lose appetite and stuff like that. That'll be another reason why people lose weight in MDS because sometimes it's treatment related. Sometimes it's the disease itself.

**Q8:** (inaudible 34:05)

**Arun Sunny, PA:** It's... So, it's two different issues actually. It's (inaudible 34:15) and weight loss. Loss of appetite is two different things.

So, what we can do with if someone experience fatigue? So, some people... for every patient MDS is very unique for different patients. MDS is unique. So, some of it 5Q they usually are transfusion dependent. So, usually give them a lot of transfusions and stuff like that. Sometimes as Dr. Shastri told you white counts are low we give them growth stimulating factors like Neupogen and stuff like that. That's how you treat neutropenias and stuff like that.

So, this is some of the symptoms that patients who actually MDS they will tell you. My friends don't understand what's wrong with me. They say I look fine. I can't even walk up the stairs without stopping and getting my breath. I can't play with my children. I'm just too tired. So, all these are some of the... some of the complaints my patient tells me when I see them in the clinic.

So, I want touch upon fatigue for (inaudible 35:50) fatigue is 2.2 (inaudible 35:55 – 36:04). I want to touch base on what causes too stress in MDS patient. So, the first thing I want to touch upon is (inaudible 36:11). So, if someone is diagnosed with MDS what's the worst fear that we could potentially have? When someone is diagnosed with MDS what is the main cause of concern? So, yeah. That's definitely a concern, but with MDS. The main thing worry about, they worry about am I so... a lot of educated patients they know it's a preleukemic condition. It's a preleukemic condition. That's the main thing they worry about. So, someone has MDS they don't know... (inaudible 36:53) leukemia (inaudible 36:55) worry about and they... that's a very... that's the question I get every day when I'm at the clinic. Am I a leukemia? So, am I there yet? So, a lot of reassurance is needed with patient with MDS. So, they always think about what could go wrong and a lot of people with MDS they have... They're on Vidaza, all this chemotherapy and Vidaza itself it takes four to six cycles of treatment for them to get some response and they are always worried about am I going to respond to Vidaza? There's another cause of distress in MDS patients, but the family (inaudible 37:46). So, MDS plays... it requires... a lot of people are fatigued and it's a disease of the elderly people around 60 – 65 and they always like worry about who's going to bring me to the clinic, who's going to (inaudible

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38:07) to the clinic and stuff like that. So, am I troubling my family? Am I troubling my son who has to work? They had to take off work and stuff like that. So, they always have worry about the family issues. So, some people... some people when they get diagnosed with MDS they used to be like a lot of fit and stuff like that then once they have the MDS... when the MDS diagnosis they... it takes effect on their physical and emotional well-being and they don't feel like themselves anymore. The main thing here we have to worry about in the Bronx is the finances. That's one main thing you got to worry about. These patients they're on Vidaza. It's not a cheap drug. They come to us with all this billing issues and stuff like that. So, that's a cause of distress in MDS patients. So, do you have any questions about any of the distresses or...?

It's being educated. That's the main... (inaudible 39:31 – 39:40) I'm so sorry. It comes and goes. I'm so sorry. I don't know what's going on with this. On top of that I'm nervous. So, that's another... on top that I'm nervous.

(inaudible 39:53 – 41:12) cancers (inaudible) and sometimes it'll (inaudible) is stress. That doesn't necessarily (inaudible) medication (inaudible) being talked to and (inaudible) because of contact (inaudible) program and find them a buddy, somebody that's (inaudible) another thing that (inaudible).

I'm sorry. I'm taking some of your time...

**Arun Sunny, PA:** No, no, please.

**Aditi Shastri, MD ?:** But I really care about this which is (inaudible 42:52) financial (inaudible) is very (inaudible) So first of all if you're suffering because of your medical care feel free to talk to your medical team about it because we have access to (inaudible) so what I actually did for my patient is (inaudible) able to actually find a way (inaudible) subsidize (inaudible) medication because it turned out it was not the MDS medication (inaudible) your physician. (inaudible) and I worked with that other provider (inaudible) were able to finance that medication for their patient. So, he was that (inaudible) but (inaudible) he actually told them that I couldn't do anything about it (inaudible)

**Q8:** (inaudible) changed. The patient doesn't even know it (inaudible)

**Arun Sunny, PA:** (inaudible) with that diagnosis of MDS. So, (inaudible 45:01 – 45:21)