

Speakers:

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Aditi Shastri, MD: So, I'm just going to talk about how we treat MDS and, again, it's really very casual. So, if you have any questions just feel free to interrupt me. I will be going through clinical data, so if it gets heavy or you don't understand something just feel free to ask.

So, I don't... I will be using some trade names of drugs because you may be familiar with those names, but my slides are free of any commercial bias.

So, I'm going to skip some of these slides because Dr. Verma has already gone through an introduction about MDS and risk stratification, but where I want to start is over here. So, you already got a lot of information about the fact that there's different risk categories of MDS and we have other tools to give us information which includes molecular information about the deletion 5Q-. These molecular mutations.

So, how do we actually decide what do we do, where do we go from here? So, how do we tailor therapy for patients with MDS? So, there's definitely several factors that we consider when we make this decision so and you make this decision with your clinical team. So, basically we look at what is the risk category of the patient. Are they low risk or lower risk disease or are they more higher risk disease or higher risk MDS? What comorbidities does the patient have? So, in addition to your MDS what other problems do you have? I mean, somebody might have hypertension or diabetes or more serious things like advanced chronic kidney disease or advanced Crohn's disease and these things play a role in decision making for treatment and in addition to extending the life of a patient we also have to focus on making patients feel good. You should be able go about your daily activities and that's a goal of treatment. So, managing symptoms is important and another very important thing to consider is how easy is it for a particular patient to tolerate the treatment? So, for example, I have some patients who live far away and they really don't want to come very day for getting intravenous chemotherapy. So, for these patients taking chemotherapy in a pill is actually much better for them and then they come and see me once every two – three weeks versus somebody that lives really close to the hospital and really doesn't mind coming, say, seven days a week for intravenous chemotherapy. So, this is something we have to take into consideration and I'm going to talk about low risk MDS first. So, there's definitely, again, several different ways to treat it and you and your clinical team make this decision together. So, we have transfusion support, growth factors, the drug that was mentioned by Dr. Verma, Lenalidomide or Revlimid. Another drug called Azacitidine and clinical trials.

So, treating the cytopenias is very important. So, as was previously explained Myelodysplastic Syndrome Myelodysplastic Syndrome Myelodysplastic Syndrome causes your bone marrow to not really function that well and you end up having these low blood counts and they can basically globally affect your blood. So, all your counts may be depressed or maybe just one cell line may be down. So, for patients that have anemia we do give them red blood cell transfusions and these are definitely timely and required, but can have the side effects of sometimes you could have a transfusion reaction from it. A lot of red blood cell transfusion eventually builds up the level of iron in your body. The levels of iron go up and this can affect important organs like your liver and your heart and sometimes people can have what we call volume overload where they have swelling in their feet in more volume that they... more than they need. You can have low white cell counts. Your white cells are important for fighting infections and it's your immune system. We don't really transfuse when you have low white cells, but what we do is give growth factors. You might have heard of drugs called Neupogen or Neulasta. So, these are drugs to get your blood counts up and also antibiotics to prevent you from getting any serious infections and, again, you could have side effects from these treatments which include having headaches, joint pains, muscle aches, some of the antibiotics could give you side effects and the other important cell line is your platelets. Now, platelets are very important because they help the blood clot. Otherwise we would end up bleeding from like minor scratches. So, when your platelet counts are down you could have bleeding very easily and we give platelet transfusions to prevent this and, again, side effects from getting these platelet transfusions involve having transfusion effects. Sometimes it could be really a very big allergic reaction that we call anaphylaxis. That is you could suddenly get pretty sick from that. So, just some things to keep in mind while you're getting transfusions.

Now, growth factors are very important in Myelodysplastic Syndrome. Some of you might have received some of these growth factors or at least heard the names being thrown around. So, when the red cell counts are down and they're not so bad that you immediately need a transfusion your doctor might say, well, you could benefit from a red cell growth factor that will keep the blood counts higher and these may be Epoetin or Procrit, Darbepoetin or Aranesp. There's white cell growth factors that we just talked about. So, these are, again, injectibles. So, there's Neupogen which are given as a daily injection and then there's Neulasta which lasts for a longer time can be given once every three to four weeks and then for the platelet growth factors we have an interesting one. We have this drug called Promacta or Eltrombopag which is actually it's an oral drug. It's a pill that is taken every day and there's another drug which is also given subcutaneously called Nplate or Romiplostim. So, you might have heard these names or you might actually be on some of these which is a great adjunct to the treatment that you're getting and sometimes the treatment itself.

Now, Lenalidomide or Revlimid. This is a very important drug for treating low risk MDS and especially the type of MDS that was previously mentioned the one that is associated with the specific mutation, the deletion 5Q abnormality, and the way that this drug actually works is that it inhibits the blood supply to a tumor. So, a tumor is usually vascular, needs a lot of blood

supply. It cuts off the blood supply to the tumor and it also actually plays a role in modulating your immune response. So, your immune cells... sometimes some of your immune cells can help the cancer escape which is how it grows, but this drug actually works against these immune cells and is really shown to be really efficacious specifically in this type of MDS, the 5Q- syndrome. It is approved for use in MDS as well as another blood cancer called multiple myeloma.

So, this is an original study which got this drug Lenalidomide or Revlimid approved. It was reported in the *New England Journal of Medicine* in 2006. So, here all patients that had low risk MDS with the specific abnormality, the deletion 5Q and those that were dependent on red blood cell transfusions and had a good platelet count and good neutrophil count were registered and were given this medication. Either they were given the drug continuously at the dose of 10 milligrams every day or some patients even got it at like 10 milligrams every day for three out of four weeks in a month and at 24 weeks the response was assessed and they wanted to see if these patients were actually able to become what we call transfusion independent. That is they could live without getting red cell transfusions and it was very interesting to see that of all the patients that got this drug about 76 percent of all comers had a response in the term of their red blood cell count actually went up and about 73 percent patients actually had a response in their disease status. That is the abnormal chromosomal, the karyotype that they had actually regressed. So, this is some of the data from this study which shows that the hemoglobin went up by on an average five grams per deciliter. The time for response was 4 ½ weeks and the duration of response was more than two years. So, this drug is really very efficacious and we use it routinely to treat the deletion 5Q- MDS.

Now, what about low risk MDS patients that don't have this deletion? What do we do for them? Which is most of them because this deletion is present in about 25 to 30 percent of patients with low risk disease. So, patients that don't have the deletion were also actually evaluated in a clinical study. They looked at the same parameters that is patients who had low risk MDS, people that were transfusion dependent and had a good platelet count and white cell count and they gave them the drug in the same exact way and they did see that there was a response in terms of the red cells as well as a disease response which was about 43 percent and 19 percent respectively, but it wasn't as dramatic as we saw with the deletion 5Q-, but it did have some response. So, the median increase in the hemoglobin was 3.2 grams per deciliter, the time to response was 4.8 weeks and the duration of response was about 41 weeks. So, it works but not that great for patients that don't have this deletion and some side effects to keep in mind if you're on Revlimid is that there is a risk of getting low platelet counts. So, thrombocytopenia or neutropenia which is a low white cell count and these are the most common side effects.

Now, this is just a little treatment algorithm for the patients that don't have the deletion 5Q. What other options do we have to treat these patients? Now, in these patients we actually check the hormone levels of a hormone called erythropoietin. This is a very important hormone that we all have and it actually helps us to keep our red cell counts at the level at which they are. It helps to regulate our hemoglobin and sometimes patients with MDS can have low levels of this

hormone erythropoietin which is how we check the levels and if we see that the levels are less than 500 then we treat these patients with Erythropoietin or Darbepoetin. These are like exogenous agents which actually work like the hormone that we have. So, we're just kind of supplementing a low level of hormone and for patients that have a normal level of erythropoietin these patients don't really benefit from getting erythropoietin exogenously. So, for these patients we use a different type of treatment that is called a hypomethylating drug. You might have heard your doctor's use this term. So, Azacitidine or Decitabine and transfusional support.

So, I just want to talk to you a little bit about Erythropoietin. So, this drug has a response rate of about 20 percent in patients with MDS and those that obviously have a low level of this hormone in their blood respond better. Those that have a lower risk of MDS respond better and when it's given in combination with a growth factor with G-CSF which is also called Neupogen or Neulasta then the response is better. Now, for patients that are not a candidate for erythropoietin, like I said, there's some other options. So, there's one option which is immunosuppressive therapy. So, some patient with MDS will respond to this and there are two drugs here. There's a drug called antithymocyte globulin which is given intravenously or ATG and there's another drug which is given in a pill form called cyclosporine and a small subset of patients with MDS will respond to these drugs. Age is very important variable in considering who to give this treatment. So, patients less than age 60 respond best to this treatment. We also check a genetic status. We also check the genetic status of this marker called HLA-DR15. So, if you do have this positive then you have a better response and if you do end up responding to this treatment then this response is really long lasting, but keep in mind just a small subset of people respond to this treatment. The other option is the drug I told you about hypomethylating agent. Some people may even call it chemotherapy, but this a drug that we... these drugs are Azacitidine or Decitabine and in low risk MDS, there's the different schedules that people are using. So, if you maybe took a second opinion and another doctor gave a different dosing schedule that's not necessarily wrong because we're still experimenting as to what's the right dose and the duration.

So, I just want to talk to you a little bit about Azacitidine because this is more commonly given in the low risk patients. So, this is a drug that works directly on your DNA. So, the DNA is abnormal in these stem cells that have MDS and this drug works directly on the DNA and it actually targets the abnormal cells more than the normal cells. So, in a way it's very specific to those cancer cells. So, it's a good drug for patients with MDS and it's approved for patients with low risk as well as high risk MDS.

Now, I just want to skip over to high risk disease. So, again, some of the drugs that you heard... Yes?

Q1: (inaudible 16:23)

Aditi Shastri, MD: This one?

Q1: (inaudible 16:27)

Aditi Shastri, MD: Yes.

Q1: (inaudible 16:28)

Aditi Shastri, MD: Yeah. No problem Go ahead. I'm sorry. It's a little busy. I didn't like go through all the details.

Yes, hi.

Q2: Why don't you ever use a stem cell transplant in patients with low risk MDS? I mean, I realize there's very serious side effects to stem cell transplant including death. However, (inaudible 17:18) with low risk MDS in certain patients and particularly if you have (inaudible 17:25) even (inaudible 17:27). I mean, it could really really turn into a vampire. Why not use it?

Aditi Shastri, MD: So, you know what?

Q2: Or at least the option to the patient if they want to risk (inaudible 17:41).

Aditi Shastri, MD: I think you really asked a great question to be honest and I agree with you sometimes patients who have low risk MDS and are transfusion dependent really can have a very poor quality of life because of the frequent transfusions that they have to get and frequent doctor's visits and blood counts.

Q1: Transfusions only take you up a hemoglobin of 10 which is (inaudible 18:09).

Ira Braunschweig, MD: (inaudible 18:10) I think it's a very important question and when we say that one is low risk, high risk and what our recommendation is it doesn't mean that the individual patient can't say I know the risks about a transplant, but I... my life is not... the quality of life that I have currently is not acceptable and I'm going to accept that risk, those risks, and want to... I'm going to go for a possibly curative therapy. I think that's the answer.

Q1: Well, the point is (inaudible 19:23) they give you are risky.

Ira Braunschweig, MD: No.

Q1: (inaudible 19:30) therapy.

Ira Braunschweig, MD: I think that's very important that an MDS patient has to be aware of their options and being participating in something like this is a great way of doing it and they

have to be... an MDS patient has to be an advocate for themselves and if they say I really want to consider... I want to speak to a stem cell transplant physician about this option then there better be at least okay, here's a referral to one. I'm going to send you to a stem cell transplant physician to explore that possibility. So, the... I'm going to show you a slide in a couple of minutes and I'm sorry, Aditi, but...

Aditi Shastri, MD: No, no, go ahead.

Ira Braunschweig, MD: But I think that it's very good...

Aditi Shastri, MD: It's a good discussion. Yeah.

Ira Braunschweig, MD: I want to have an interactive discussion that transfusion dependency is an indication for a referral for a stem cell transplant. So, it's really very accepted that that should be the case. So, I think an MDS patient has to advocate for themselves and say I want to see a stem cell transplant physician and if you don't get me to one I'll find one myself.

Q1: (inaudible 20:48)

Ira Braunschweig, MD: Absolutely.

Q1: Can I ask you (inaudible 20:52)

Aditi Shastri, MD: Yes.

Q1: Do you work in (inaudible 20:54)

Aditi Shastri, MD: Yes. So, there's some things that predict for a better response. There may be an odd case that will respond over the age of... but typically patients younger than age 60 are the ones who respond best to this ATG and cyclosporine. Very rarely cyclosporine alone. Yeah.

Q1: So, this (inaudible 21:19). Is it such that you (inaudible 21:28) something else or it (inaudible 21:32)

Aditi Shastri, MD: Yeah. So, for the patients that respond and like I said sometimes these patients can have a long response. The treatment is tailored a little bit to how the patient is doing. So, if somebody's been on the drug already for... Obviously, once they have a response we start tapering the drug back. We start cutting back the dose of the cyclosporine and if they've been a year or so out I think we could give them a fair chance of being off the drug as well. What do you think? I mean, I just tailor it based on the patient is doing. Yeah.

Amit Verma, MD: So, the cyclosporine. So, Studies have shown as far as a specific type of MDS. We already (inaudible 22:28) the bone marrow... we look at the bone marrow. It appears empty because hypoplastic and that is the kind of MDS patients that we consider for this cyclosporine and I would say not for (inaudible 22:48) percent (inaudible)

Aditi Shastri, MD:

Q2: I had (inaudible 22:54) that's not (inaudible)

A: So, the concept is then you could have a type of MDS where the only use is trying to kill your stem cells and these drugs (inaudible 23:08) cyclosporine. Now, this could be preventing the immune system from attacking (inaudible). So, that's what's causing the damage (inaudible 23:15), but (inaudible) stem cells the cells have (inaudible). It's not the immune system. That is something (inaudible) cells and then we have to use a different strategy or just change them all together with the stem cell transplant (inaudible 23:33)

Aditi Shastri, MD: Yeah. So, that's pretty much it. I don't have more to add. Do you have any other questions? Okay.

Alright. So, we'll just talk about high risk MDS really quick. So, again, going to just touch upon some of the drugs we already talked about, Azacitidine and Decitabine. Dr. Braunschweig will be talking about stem cell transplant or what we call an allogeneic bone marrow transplant. So, I'm not going to dwell on it and clinical trials. So, these are really the options for patients with high risk disease.

Now, I just wanted to show you a little algorithm for how kind of triage patients as to who would be a good candidate for what kind of treatment. So, if you're already... right at the get go looking at the patient's risk status, their medical comorbidities, what other diseases they have we do go ahead and decide... make a decision with the patient about whether and also a very important factor is the availability of a donor, a stem cell donor. So, does this patient have siblings or children or parents that could be a stem cell donor or maybe an unmatched donor from the marrow donor program? So, do they have a donor or not. Now, if they don't have a donor then we kind of continue treatment with these drugs Azacitidine and Decitabine for a long time or sometimes we can put them on a clinical trial up front. Most of the times what we do is we give them a shot with the Azacitidine or Decitabine. If they're responding well and great. If not then we give the option of a clinical trial.

Yes?

Q3: Is there an age that you cannot get a bone marrow transplant? Are we too old at some point?

Aditi Shastri, MD: Yeah. So, I think Dr. Braunschweig will talk about it some more, but in a nutshell there is no actual age at which you can be said to be ineligible for a bone marrow transplant. You just have to consider many factors like I said. Your physiological age is more important than your actual age.

So, this is actually I just wanted to show you guys the trial that was done with Azacitidine. This was back in 2009 which led to the approval of the drug. So, here this was what we call a randomized trial. That is some patients got Azacitidine, but some patients got a treatment that was assigned by the physician that was different from Azacitidine. So, different type of chemotherapy or just maybe transfusional and growth factor support and the patients that got Azacitidine got it for seven days and here we see this was actually something which was very remarkable. We found that Azacitidine actually improved the survival of patients with high risk MDS. So, on an average the green line is the patients treated with Azacitidine. These patients lived about 9 ½ - 10 months more than the ones that weren't treated with the drug.

So, Decitabine is the other drug or the other option and here there've been two large studies which have looked at this drug and it has a really... it has an improvement in the response rate compared to other... what we call best supportive care. So, best supportive care just basically means transfusional support, growth factor support, just to... just supportive care in general and there've been multiple response rates that have been reported in different clinical trials. Sometimes they can range from 20 percent to 60 percent. So, there's a huge range in response. In high risk MDS we haven't seen yet an improvement in overall survival with Decitabine. That being said there's a significant amount of research and interest in this drug. So, I think the information about this drug is really evolving at this time and typically your doctor might recommend giving it to you over five days. Some patients might get it over 10 days depending on what their molecular profile is. So, like Dr. Verma mentioned if you have some of these mutations like P53 or the TP53, your doctor might recommend a long duration of treatment with Decitabine.

So, after we've exhausted this option of the hypomethylating drugs, Azacitidine and Decitabine, you have other options available to you. So, we go back to the bone marrow transplant and like Dr. Braunschweig said this is really the only curative option available at this point for MDS patients and also I think it's very important to talk... I'm sure if your doctor will bring up the option of a clinical trial. If they don't then I think it's important to be an advocate and just kind of bring this up and they could refer you to a center that has trials if they don't have it over there or not. So, these are things to keep in mind.

Just want to talk for just a minute about transfusion dependency. So, like I mentioned previously patients that get a lot of red cell transfusions can end up having a lot of iron that gets deposited in the body and when this iron gets deposited in your body it can cause several organs to really not work well. So, the chief among them is your liver. So, a lot of iron gets deposited in your liver, in your heart, in different organs and you can end up having pretty severe side effects related to

this high iron in your body and for this... for patients that have this need for transfusions we worry about them building up this iron and we give them drugs that you might have heard called chelating agents. We say they're iron chelating agents. So, you might have heard their names, Deferasirox, Deferiprone. Your doctor might have spoken to you about them. So, we always check the patient's ferritin levels, the patients that are on these transfusions and different committees have different guidelines. So, the NCCN says more than 2,500 of a ferritin. The MDS Foundation says more than 1,000. These patients should be considered to get this iron chelating therapy. That is the treatment just binds this iron and prevents it from getting deposited in different tissues in your body.

Q4: Do you think a clinical trial (inaudible 30:55) recommend treatment. Is it something that you have to ask for or are you automatically (inaudible 31:06) in a clinical trial?

Aditi Shastri, MD: No. So, you're never automatically in a clinical trial. It's something that is always discussed with you hopefully at... if there is a stage in your treatment that's a good option for you. Your clinical team should be talking to you about it. You could definitely... you should definitely bring it up if that's something you feel you're eligible for at that time, but a clinical trial is always done with a good amount of information given to you about the study, a good amount of time given to you to find out a little more, talk to your family about if this is a good option for you and whether you should go ahead with it and there's different types of trials which Dr. Verma will be talking about. There's some trials which are early, more early phase. That is pretty much all the patients... all the patients getting on the study will be getting the drug. Some studies are what we call late phase where we will... you might be randomized. That is some people will get the drug and some will be on another arm which won't get the experimental treatment. So, I think all these factors have to be discussed and are discussed at great length before you enroll in a clinical study.

So, how can you help yourself? So, definitely keep up with any physical activity that you've been doing. Try to. Obviously, there will be days when you've undergone chemo you feel so tired you don't even want to go get a glass of milk, but that's okay. Listen to your body, but I think it's important to always try and keep as active as you can. It's important to watch what you're eating and because your fitness does play a role too in how you tolerate chemotherapy and a stem cell transplant and I just wanted to offer you some additional resources. So, the MDS Foundation they're very active on Twitter. They have different forums going on and you could find out more about this. They have a Facebook website. You could follow me on Twitter. I kind of put out some MDS related information many times and if you have any questions ask your doctor. Don't ask Google and ask your treatment team.

(Applause)