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A Look Behind the Curtain: *Exploring Lower-Risk MDS-RS & MDS/MPN-RS-T*

Announcer:
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[CHAPTER 1]

Dr. Garcia-Manero:
We're still facing challenges in optimizing outcomes for patients diagnosed with lower-risk myelodysplastic syndrome (MDS)-associated anemia. In this first chapter, we're taking a closer look at the diagnosis and multidisciplinary management of this condition.

This is CME on ReachMD, and I’m Dr. Guillermo Garcia-Manero.

Dr. Komrokji:
And I'm Rami Komrokji from Moffitt Cancer Center. Guillermo, it’s always good to brainstorm with you about MDS and those topics.

So maybe you can explain to our listeners your approach in establishing the diagnosis, the team effort to put in, what are the variables you evaluate to help you to risk assess the patients, establish the diagnosis, and then start thinking of the treatment?

Dr. Garcia-Manero:
I believe this question that you just posed is actually one of the most important things that probably you and I do at Moffitt or at MD Anderson, that is, confirming the diagnosis. So we know from past experience that there is a significant rate of discrepancy from one center to the other, and potentially centers that have larger volume or more dedicated hematopathologists can really help with this diagnosis.

This is fundamental because these assessments on bone marrow aspirations, biopsies are going to really determine what we do as hemato-oncologists. They are going to help us confirm diagnosis, grade the disease, and then hopefully make the proper therapeutic decision. And this requires this team effort between the hematopathologist and, in this case, the hematologist.

So you have to have access to a good specimen, meaning a good bone marrow aspirate and bone marrow biopsy. This will give you the morphology and the diagnosis.

But what has become very clear is that, of course, you need a sample for cytogenetics. That's fundamental to really assess the prognosis of these patients. And more and more over the last 10 years, but even more recently in the last few months, it has become clear that the molecular or genomic annotations of these specimens is fundamental. Indeed, there is a new classification known as the IPSS-M [International Prognostic Scoring System – Molecular] that allows you to predict prognosis based on the mutational events that you may see in these bone marrows. So most of us do that by some type of next-generation sequencing assay that covers, hopefully, most of the genes that are relevant in this disease.

As an example, actually, how important this is, is that there are now some entities that actually are probably described on their – entirely based on specific mutations. An example, for instance, is the presence of SF3B1 mutations. This gene is the most commonly mutated gene in MDS; it's a splicing-related gene. It's associated with a particular type of myelodysplastic syndrome, where you have excess ring sideroblasts. We used to call these refractory anemia with ring sideroblasts. And these patients have particular natural history, and they may actually respond differently to the specific forms of therapies that we're going to be discussing through the rest of this conversation.

And indeed, actually, if you have a presence of this SF3B1 mutation, you may overrule some of the requirements in terms of percentage of sideroblasts that were required in the past to really call this.

So this is an example that is key from a very frequent mutation that basically gives a proper diagnosis and will guide the clinician in terms of the proper therapeutics once you establish that.

Dr. Komrokji:
Absolutely. I totally agree.

And to your point, I think we have newer classifications. There are some discrepancies, but what is clear, that is, you know, kind of unified vision on the molecular classification. So both newer classifications established SF3B1 as a unique entity. And as you mentioned, this is not just a pathological classification; this has some treatment implications. So the SF3B1, now we have an option of treatment for those patients with deletion 5q who've had lenalidomide. So the pathological classification is not anymore just for the heme-path people, but it has some implications for the patients.

So maybe you can summarize or give us your take-home message from this discussion.

Dr. Garcia-Manero:
The take-home message will be that you really need morphological diagnosis by an expert pathologist or the aspirate biopsy. And perhaps the ultra key takeaway message from here is that when you do that, you really need to have proper cytogenetic and molecular next-generation sequencing results to really come with a diagnosis and inform the patient.

Dr. Komrokji:
Absolutely, I agree. I think my take-home message is always spend time in establishing the diagnosis, rule out things that look like MDS, get the molecular data, and then get a baseline or sense of the disease behavior.

So in Chapter 2, we'll be discussing how to more quickly recognize ESA [erythropoiesis-stimulating agent] failure and who are refractory to ESA treatment, so stay tuned.

[CHAPTER 2]

Dr. Komrokji:
Welcome back. So in Chapter 2, we are looking at how to use erythropoiesis-stimulating agents, or ESAs, to treat patients with lower-risk MDS and how to assess when you should move beyond ESA.

Dr. Garcia-Manero:
Dr. Komrokji, continuing from Chapter 1, what are the challenges in achieving transfusion independence in lower-risk MDS? And how do ESAs fit into the treatment paradigm? Lastly, how quickly are we able to recognize patients who are failing ESA therapy or who are refractory to ESAs?

Dr. Komrokji:
So the first, obviously, in my mind is when to pull the trigger on starting treatment. You know, obviously, there is no magical threshold of hemoglobin to consider. Most people will consider around roughly 9, but it really relates to the patient's symptoms, impact of the anemia on the quality of life. And obviously, erythro-stimulating agents are the mainstay for treatment of anemia in lower-risk MDS.

There are simple ways to predict the chances of response or whether we can skip that step. So, for example, an endogenous serum EPO [erythropoietin] level more than 500 needing more than 2 units of red blood transfusion per month really predicts less than 10% chance of response to ESA. But in other patients, if they are not heavily transfusion dependent you know, anemia is progressing, they are a very reasonable first step.

And as our audience knows that there are 2 formats of them: the erythropoietin format, which is given weekly, and the darbepoetin, which is given every other week. It's really a matter of dosing equivalence between the two, no big differences. Doses in MDS should be on the higher range, 40- to 60,000 equivalent of erythropoietin. And we will try them somewhere around 6 to 8 weeks. And if there is no response, then we should be moving earlier.

And that creates a dilemma because I think many times we see a lot of patients that are continuing erythroid-stimulating agents in spite of receiving blood transfusions on a very regular basis with the thinking that maybe it's even slowing it more. But if a patient is receiving blood transfusions on a monthly basis, I don't think that ESAs are helping. So obviously the clear criteria of ESA failure, somebody that had a secondary failure, was responding, and the hemoglobin is dropping after that. But obviously the challenge with those patients if their hemoglobin doesn't go up and they are still needing to do blood transfusions, I think those patients are not benefiting from the treatment, and it's usually time to move to the next therapy.

I also obviously reflect on the impact of the ESAs on the quality of life for patients. You know, if they're not needing transfusions or their hemoglobin is improving, are they feeling better? But the most probably common pitfall I see is this continuation of ESA while patients are receiving probably the same transfusion burden or transfusions with the notion that maybe it would be worse if they stopped the ESA.

Dr. Garcia-Manero:
For those just tuning in, you're listening to CME on ReachMD. I am Dr. Guillermo Garcia-Manero. And here with me is Dr. Rami Komrokji. We are discussing multispecialty management of patients with lower risk MDS with a special focus on the treatment of MDS-associated anemia.

Can you then tell us, Rami, if there are any next-line treatments already in place or coming for our patients? And perhaps what is their mechanism of action?

Dr. Komrokji:
Absolutely. So, for example, if ESAs are not working, the next question we always ask, do the patients have deletion 5q? And for those patients, lenalidomide had been established as the treatment of choice.

Nowadays, and the next question after that, do patients have ring sideroblasts or the SF3B1 splicing mutation that you mentioned earlier? And for those patients, now we have luspatercept approved by the FDA for patients that are transfusion dependent. Luspatercept is a first-in-class drug that works as erythroid-maturating agent. So it works at a different stage of the erythropoiesis. It's a fusion trap protein that bind ligands that activate TGF-beta pathway that are critical in the terminal erythroid differentiation. So this drug is approved for those patients.

For other patients, sometimes we still use lenalidomide and the non-del 5q hypomethylating agents, which you've pioneered use in lower risk in many studies looking at patients that have some higher-risk features, or concomitant other cytopenias.

But for anemia, I think the most critical question after ESA failure is do patients have deletion 5q? And if not, do patients have the splicing mutation SF3B1? Or do they have ring sideroblasts? Because now we have options tailored particularly for those subgroups.

Dr. Garcia-Manero:
Thank you, Rami. This really has been great. But many, many times in our practice, we see patients that clearly are not benefiting from these ESAs that are still on those compounds.

Dr. Komrokji:
Yeah, I agree with you. If those agents are tried for 6 to 8 weeks and there is no response, one should move on.

Dr. Garcia-Manero:
I totally agree with that.

In Chapter 3, we'll be discussing an interesting new agent for use in patients who have not responded or are refractory to ESA treatment. Indeed, Dr. Komrokji already introduced us to this agent: luspatercept. Stay tuned.

[CHAPTER 3]

Dr. Komrokji
Welcome back. In Chapter 3, we are discussing when to incorporate a novel evidence-based therapeutic option for patients with lower-risk MDS who are not responding or are refractory to an ESA.

So, Dr. Garcia-Manero, we introduced luspatercept in Chapter 2. Let's dive a bit deeper in the clinical trial data for this agent, namely the MEDALIST and COMMANDS trials. What is the greatest value for this agent? You and I had been part of those trials. You have amazing experience using this drug. So maybe you can summarize your point of view.

Dr. Garcia-Manero:
Thank you, Rami. You did a fantastic introduction in terms of the mechanism of action of luspatercept, and indeed, you were the leader

of the studies in North America. So these drugs, as you mentioned earlier, affect this terminal erythroid differentiation pathway by modulating TGF-beta signaling. And of course, this was extremely exciting for us because of a number of data from animal models, phase 1 trials, etc.

And eventually, we designed this clinical trial known as the MEDALIST trial. So this is a very important study, it was published in *The New England Journal of Medicine*, and it was actually presented as a plenary talk at ASH around 3 years ago. And it led to the approval of luspatercept for patients with lower-risk MDS with an SF3B1 mutation or with ring sideroblasts that had already received an ESA and were transfusion dependent. So this is very important for us.

So let's talk about this study. So basically, what we did here was identify a subset of patients with ring sideroblastic anemia with or without this SF3B1 mutation that were transfusion dependent, had already received an ESA, or were thought not to be candidates to an ESA because they, say for instance, they had a high EPO level. And then they were randomized in this placebo study between luspatercept or a standard of care that will be continued supportive care with transfusions. So this was a very well-designed international trial.

And in this study, we saw 2 things. Perhaps the least important that is this drug is extremely well tolerated, although we'll discuss in a minute some potential issues with fatigue. But the key issue is that we saw a significant improvement in transfusion independency in those patients that received luspatercept versus those that did not. So that was really important.

Furthermore, we saw that those patients that had that response to this compound actually had durable responses. And they had what we call a metallurgical improvement, meaning that the hemoglobin increased. So this is really, in summary, the key issues or the key results from this MEDALIST trial. And again, this led to the approval of luspatercept for our patients. And this was extremely exciting for us, because after 14 years, this was 1 of the 2 drugs that we got approved a couple of years ago for patients with MDS, something that we have not seen almost in 15 years, as I just said.

Now, one thing that we learned from the MEDALIST trial that is really critical is that, as you will expect, the rate of responses was a little bit different in patients that had received fewer transfusions compared to those that had received a more significant transfusion burden, let's say more or less than 4 units at the time of starting this trial. What this meant, and we had seen some of this in some of the studies, Rami, that you have conducted early on, that is, potentially, those patients in an earlier stage of this disease could really benefit significantly from luspatercept. And indeed, actually, that concept in particular, supported by the lack of toxicity, led to the design of this trial that we call the COMMANDS trial. So this study is actually still ongoing. It's almost reached its accrual. And this is a fundamental study where we are randomizing between luspatercept versus an ESA for any patient with lower-risk myelodysplastic syndrome that is transfusion dependent of red cells that has not received prior therapy. So this is basically first-line therapy for patients with transfusion-dependent lower-risk MDS.

Again, we don't have the results of this trial. But my expectation is that the results of this study could be really transformative, and they may establish a new frontline therapy for anemia in patients with lower-risk myelodysplastic syndrome. Now, we need to wait for those results.

One thing that, actually, I would like to mention as we close this part is that we have also observed with luspatercept a subset of patients with MDS that had achieved bilinear or trilinear responses with luspatercept, indeed actually, this was published in *Blood* by Dr. Komrokji and myself a few months ago.

So some of these patients with luspatercept may have some occasional benefit that goes beyond anemia that may affect platelets or the white count. So we really need to learn more about this.

And then in the future, I see luspatercept actually moving to even earlier stages, to patients that are transfusion independent with significant anemia. So I think we're entering a new era of the treatment of anemia for patients with lower-risk myelodysplastic syndrome.

Dr. Komrokji:
Absolutely, I totally agree. Thank you for this great overview. A key point is also the dose escalation. Particularly, as Dr. Garcia-Manero mentioned, the most important predictor of response is the transfusion burden. So in patients, if they are, like, more on the side of heavy transfusion burden, most of those patients will need the dose escalation. This is one of the pitfalls we still see, that the dose escalation is not done appropriately, particularly in patients that are on the side of more heavy blood transfusion.

Dr. Garcia-Manero:
As we close this, Rami, I would like to emphasize a couple of things that you said that are very, very important, if you'll allow me. So first of all, this issue of the dose escalation of the luspatercept, this sometimes, because the drug is relatively new, I say that in the community you may need some extra education, realizing that sometimes you need to increase the dose, as you said, from 1 to 1.33,

1.75. That's very important.

The other issue that we learned is that, in the MEDALIST trial that, you know, for patients who were transfusion dependent and had already received an ESA, so this is a different group of patients than the COMMANDS, occasionally they may need a transfusion here and there. And in my opinion and experience, this doesn't mean that the luspatercept is really, you know, not working anymore. You probably need to push it a little bit, as we have done with the ESAs for a long period of time.

And then this issue of fatigue that we see in the first couple of months, but then eventually, I think, patients recover from that. But I really think that, you know, like with any other drug, we really need to learn how to use this compound, and this dose-escalation issue is very important.

And then to emphasize that, I didn't want to mean that we should not use this compound in patients with heavy transfusion burden, because that's really probably the best option that we have right now. I was just trying to indicate that in patients that are in an earlier stage, this drug actually works extremely well, as you will expect.

Dr. Komrokji:
Absolutely, I agree with you.

Unfortunately, that's all the time we have today. So I want to thank our audience for listening in and thank Dr. Garcia-Manero for joining me and for sharing all his valuable insights, as usual. It was great speaking with you today, Guillermo.

Dr. Garcia-Manero:
Thank you, Rami. It's always a pleasure to discuss these issues with you.

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