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Addressing Treatment Gaps in Anemia Among MDS Patients

Announcer:
Welcome to ReachMD.

This medical industry feature, titled *"Addressing Treatment Gaps Among Patients with MDS-Associated Anemia*" is sponsored by Bristol Myers Squibb.

Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to this medical industry feature on ReachMD. I'm your host, Dr. Charles Turck, and joining me today to discuss the treatment gaps in anemia among patients with myelodysplastic syndromes, or MDS for short, is Dr. Jamie Koprivnikar, who's a hematologist oncologist at Hackensack Meridian Health, and focuses on treating patients with leukemia, MDS, and related disorders.

Dr. Koprivnikar, thanks for joining me today.

Dr. Koprivnikar:
Thanks so much for having me. I'm excited to be here.

Dr. Turck:
Well, to begin, Dr. Koprivnikar, can you please tell us about your experience in MDS, and how you evaluate patients with lower-risk MDS?

Dr. Koprivnikar:
Absolutely. I've been treating patients with MDS for more than 10 years, and within my practice, I probably have at least 50 unique patients across all subtypes of MDS. My approach to a patient who I suspect to have MDS starts with really adequate and appropriate risk stratification.

And so in order to do this, I certainly am performing bone marrow biopsies, and sending that bone marrow specimen for cytogenetic and molecular level analysis. I'm also looking at a patient's cytopenias. We're looking at blast percentages on that bone marrow biopsy.

So I feel like the first step to really adequately treating our patients is to make sure we understand the risk level associated with their disease, and I do want to confirm that each patient who I'm dealing with really does have either low or high-risk disease

Once I've determined that a patient has lower risk MDS, I start to look at how it's affecting that individual, and how it might be impacting their activities of daily living. Oftentimes, what I see in my patients with lower-risk MDS is that they're experiencing anemia-related symptoms. And so I really look at whether or not the patient's needing transfusions. But even if a patient's not requiring transfusions, I do think that they may be having a level of anemia that can be impactful to their everyday activities. So, I want to also address any anemia–even that may not be associated with transfusions.

Dr. Turck:
And with that in mind, when you consider treatment for anemia in ESA-naïve, lower-risk MDS patients, what are your treatment goals, and how do you determine a treatment path?

Dr. Koprivnikar:
So that's a great question.

My treatment goals are, at minimum, that my patients be transfusion-independent because of the numerous inherent risks and inconveniences associated with transfusions. I think they're really quite unacceptable for my patients with lower-risk MDS.

Additionally, even if a patient's not receiving transfusions, I really want to avoid any anemia-driven symptoms. I know that a lot of patients, even though their hemoglobin may not be low enough for a transfusion, it may not be high enough to really allow them to run after their grandchildren, or keep up with their friends on the golf course, so I really do try to look at the way that the patient's lower-risk MDS, and in particular, the anemia associated with it may be impacting that individual's daily life.

Now if a patient has no symptoms and they're feeling fine with lower-risk MDS, I feel like that's an appropriate individual to observe, but certainly a lot of our patients presenting with lower-risk MDS may be transfusion-dependent, or again, may have anemia that is causing symptoms.

Voice Over:
The next segment will discuss Reblozyl and the Phase 3 COMMANDS trial. Reblozyl is indicated for the treatment of anemia without previous ESA use (ESA-naïve) in adult patients with very low- to intermediate-risk MDS who may require regular red blood cell (RBC) transfusions. Reblozyl is not indicated for use as a substitute for transfusions in patients who require immediate correction of their anemia. The most common side effects for patients receiving Reblozyl for first-line, lower-risk MDS are diarrhea, fatigue, high blood pressure, swelling of the hands, legs and feet, nausea and trouble breathing. Please see the landing page for additional Important Safety Information, Prescribing Information, and the Medication Guide.

Dr. Koprivnikar:
So there's been some very interesting data from the landmark phase 3 COMMANDS study that really informs my treatment of patients with lower-risk MDS who are transfusion-dependent or who have symptomatic anemia and are ESA-naïve. And so the COMMANDS study is very interesting. It basically compared luspatercept, or Reblozyl, to the prior standard of care for patients with lower-risk MDS, and that was epoetin alfa.

And so this trial had a composite primary endpoint that looked at both a 12-week, transfusion-free period in association with a 1.5 gram per deciliter improvement in hemoglobin that was independent of transfusion.

And so when measured by this composite primary endpoint, we saw that Reblozyl-treated patients were twice as likely to achieve both this transfusion independence for 12 weeks and this 1.5 gram per deciliter increase in hemoglobin, as compared to their epoetin alfa-treated counterparts.

So I think that that's really exciting news. Now, of course, we do want to look at some of the adverse events that may have been experienced by our Reblozyl treated patients. And I will mention that the most common, all-grade, adverse reactions, occurring in 10 percent or more of patients, included symptoms like diarrhea, fatigue, hypertension, peripheral edema, nausea, and dyspnea.

Dr. Turck:
So now that Reblozyl has been approved as a first-line therapy, can you share the COMMANDS trial findings that made this possible?

Dr. Koprivnikar:
Absolutely.

The COMMANDS study was a really exciting, phase 3, landmark trial that was conducted in patients with lower-risk MDS who were 18 years of age or older and who were requiring transfusion support. The COMMANDS study compared Reblozyl with the prior standard of care, which was epoetin alfa. And so COMMANDS had a composite primary endpoint, which I think was a very rigorous endpoint.

So in order to meet this composite primary endpoint, patients had to be transfusion-free for a period of at least 12 weeks. In addition to this transfusion independence, patients also had to have a 1.5 gram per deciliter or higher increase of hemoglobin that was independent of transfusional support.

Now the exciting thing about the COMMANDS study is that nearly double the number of Reblozyl treated patients met this composite primary endpoint of both hemoglobin improvement and transfusion freedom, as compared to the patients treated with epoetin alfa.

As we look at the actual numbers of patients meeting the composite primary endpoint, we see that about 60 percent of Reblozyl treated patients achieved this transfusion independence for at least 12 weeks, in conjunction with that 1.5 gram per deciliter increase in hemoglobin, versus 30 percent of epoetin alfa-treated patients.

As we look at some of the other data from COMMANDS, we see that there was a numerically longer duration of transfusion freedom in our Reblozyl treated patients. They were able to be transfusion-free for 2.5 years on average, compared to a 1.5-year transfusion-free period for epoetin alfa-treated patients.

Taking all of this together, it's nice to see that patients were able to achieve this long duration of transfusion independence, and this high response rate, with the convenient three-week dosing of Reblozyl. Now when we look at rates of treatment discontinuation between the two arms of the COMMANDS trial study, we see a higher treatment discontinuation rate in epoetin alfa-treated patients.

Now what was really driving the difference in treatment discontinuation rate was lack of response to epoetin alfa. This was the most common reason that patients treated on the epoetin alfa arm discontinued treatment. When we look at treatment discontinuations due to adverse events, disease progression and death, these were really quite similar between both the Reblozyl and epoetin alfa arms.

Voice Over:
COMMANDS (NCT03682536) was a Phase 3, open-label, randomized study evaluating the efficacy and safety of *Reblozyl* versus epoetin alfa for the treatment of anemia due to very low-, low- or intermediate-risk (IPSS-R) myelodysplastic syndromes (MDS) in patients who are red blood cell (RBC) transfusion-dependent and were erythropoiesis stimulating agent (ESA)-naïve.

The primary endpoint evaluated in this study was RBC transfusion independence (RBC-TI) for 12 weeks with a mean hemoglobin (Hb) increase ≥1.5 g/dL. Key secondary endpoints include erythroid response (HI-E) of at least 8 weeks during weeks 1-24 of the study, RBC-TI ≥12 weeks and RBC-TI for 24 weeks.

Eligible patients were ≥18 years old with lower-risk MDS who require transfusions. Patients were randomized 1:1 to receive subcutaneous *Reblozyl* (starting dose 1.0 mg/kg, titration up to 1.75 mg/kg) once every 3 weeks or epoetin alfa (starting dose 450 IU/kg, titration up to 1050 IU/kg) weekly for ≥24 weeks. The majority of study participants (>90%) were outside of the United States and a non-U.S.-licensed epoetin alfa product was used in the control arm for such patients.

At the time of the planned interim analysis (October 31, 2022), 147 evaluable patients received *Reblozyl* and 154 evaluable patients received epoetin alfa, with median treatment durations of 41.6 and 27 weeks, respectively. Results published in *The Lancet* showed:

- 58.5% (n=86) of patients receiving *Reblozyl* vs. 31.2% (n=48) of patients receiving epoetin alfa achieved the primary endpoint of RBC-TI of at least 12 weeks with concurrent mean Hb increase of at least 1.5 g/dL within the first 24 weeks (p<0.0001).
- HI-E increase of at least 8 weeks was achieved by 74.1% (n=109) of *Reblozyl* patients vs. 51.3% (n=79) of epoetin alfa patients (p<0.0001).
- Within the first 24 weeks of treatment, RBC-TI of at least 24 weeks was achieved by 47.6% (n=70) of *Reblozyl* patients vs. 29.2% (n=45) of epoetin alfa patients (p=0.0012).
- RBC-TI of at least 12 weeks during weeks 1-24 was achieved by 66.7% (n=98) of *Reblozyl* patients vs. 46.1% (n=71) of epoetin alfa patients (p=0.0003).

Patients treated with *Reblozyl* demonstrated durable responses with nearly 2.5 years of median RBC-TI ≥12 weeks (126.6 weeks, week 1 to end of treatment).

The most common (>10%) adverse reactions were diarrhea, fatigue, hypertension, peripheral edema, nausea, and dyspnea.

Stay tuned until the end of the episode for full safety information.

Dr. Turck:
So now that we have some background on Reblozyl, Dr. Koprivnikar, from your vantage point can you describe your clinical experience with this therapy?

Dr. Koprivnikar:
Absolutely. I have had a really positive experience with using Reblozyl to treat my patients with lower-risk MDS who are ESA-naïve.

The every three-week dosing is really quite convenient for my patients, but I do make sure to prepare them for the potential for taking many months to really see if they're going to have a good response to this medication.

The reason that it takes such a long period of time to have an adequate trial of Reblozyl is that there are three different dose levels that patients can potentially receive, depending upon their transfusional burden.

And so all patients start out with a weight-based dose of one milligram per kilogram. They need to receive at least two doses at this dose level, and at each dose level, before we can consider dose escalation.

Now when it comes time for patients to get that third dose, if they're still transfusion-dependent, it's important to remember to dose escalate them in the absence of any prohibitive adverse reactions.

And so you can see that as we work through all three dose levels, giving a patient an adequate trial of Reblozyl really is a bit of a prolonged process, but I think as long as we set expectations for that, both with ourselves and with the patients, that really just helps patients to know what to expect.

I've certainly seen some really positive responses. I have patients that were needing transfusions on a weekly basis prior to starting Reblozyl, who actually became transfusion-free when given an adequate trial and adequate dose escalations of the medication.

Dr. Turck:
Before we close today, Dr. Koprivnikar, is there anything you'd like to add that you'd want your colleagues or the audience listening to know?

Dr. Koprivnikar:
Definitely.

Firstly, I'd like to clarify that the COMMANDS study really opened up treatment with Reblozyl to all comers, who are ESA-naïve and have lower-risk MDS, with symptomatic or transfusion-dependent anemia. Now I know that there was an earlier approval of Reblozyl that was specific to patients who had disease associated with ring sideroblasts.

The COMMANDS study, however, looked at a much broader and more generalized patient population, however, and included patients regardless of ring sideroblast status, and regardless of mutational status. And to be clear, this has really opened up Reblozyl treatment to a very broad population of patients who have ESA-naïve MDS, and who may require red blood cell transfusions.

The other reminder that I'd just like to mention is that dose escalations tend to be the rule for patients who are receiving Reblozyl treatment. So it's just important to be aware of when a patient is due for a dose escalation and to appropriately dose escalate them.

Dr. Turck:
Those are great points to think on as we end our discussion on a treatment for anemia in MDS patients. I want to thank my guest, Dr. Jamie Koprivnikar, for sharing her insights. Dr. Koprivnikar, it was great speaking with you today.

Dr. Koprivnikar:
Thank you so much, Dr. Turck. Great to be here.

Dr. Turck:
I'm Dr. Charles Turck. Please stay tuned to hear indications and some important safety information.

Announcer:
INDICATIONS
REBLOZYL® (luspatercept-aamt) is indicated for the treatment of anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions.

REBLOZYL® (luspatercept-aamt) is indicated for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell (RBC) units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Thrombosis/Thromboembolism
In adult patients with beta thalassemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) of REBLOZYL-treated patients. TEEs included deep vein thrombosis, pulmonary embolus, portal vein thrombosis, and ischemic stroke. Patients with known risk factors for thromboembolism (splenectomy or concomitant use of hormone replacement therapy) may be at further increased risk of thromboembolic conditions. Consider thromboprophylaxis in patients at increased risk of TEE. Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly.

Hypertension
Hypertension was reported in 11.4% (63/554) of REBLOZYL-treated patients. Across clinical studies, the incidence of Grade 3 to 4 hypertension ranged from 2% to 9.6%. In ESA-refractory or -intolerant adult patients with MDS with normal baseline blood pressure, 26

(30%) patients developed systolic blood pressure (SBP) ≥130 mm Hg and 23 (16%) patients developed diastolic blood pressure (DBP) ≥80 mm Hg. In ESA-naïve adult patients with MDS with normal baseline blood pressure, 23 (36%) patients developed SBP ≥140 mm Hg and 11 (6%) patients developed DBP ≥80 mm Hg. Monitor blood pressure prior to each administration. Manage new or exacerbations of preexisting hypertension using anti-hypertensive agents.

Embryo-Fetal Toxicity
REBLOZYL may cause fetal harm when administered to a pregnant woman. REBLOZYL caused increased post-implantation loss, decreased litter size, and an increased incidence of skeletal variations in pregnant rat and rabbit studies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 3 months after the final dose.

ADVERSE REACTIONS

ESA-naïve adult patients with Myelodysplastic Syndromes
Grade ≥3 (≥2%) adverse reactions included hypertension and dyspnea.

The most common (≥10%) all-grade adverse reactions included diarrhea, fatigue, hypertension, peripheral edema, nausea, and dyspnea.

ESA-refractory or -intolerant adult patients with Myelodysplastic Syndromes
Grade ≥3 (≥2%) adverse reactions included fatigue, hypertension, syncope and musculoskeletal pain. A fatal adverse reaction occurred in 5 (2.1%) patients.

The most common (≥10%) adverse reactions included fatigue, musculoskeletal pain, dizziness, diarrhea, nausea, hypersensitivity reactions, hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection.

LACTATION
It is not known whether REBLOZYL is excreted into human milk or absorbed systemically after ingestion by a nursing infant. REBLOZYL was detected in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because many drugs are excreted in human milk, and because of the unknown effects of REBLOZYL in infants, a decision should be made whether to discontinue nursing or to discontinue treatment. Because of the potential for serious adverse reactions in the breastfed child, breastfeeding is not recommended during treatment and for 3 months after the last dose.

DRUG ABUSE POTENTIAL
Abuse: Abuse of REBLOZYL may be seen in athletes for the effects on erythropoiesis. Misuse of drugs that increase erythropoiesis, such as REBLOZYL, by healthy persons may lead to polycythemia, which may be associated with life-threatening cardiovascular complications.

Please see full Prescribing Information for REBLOZYL by clicking on the link located on the ReachMD landing page.

This program was sponsored by Bristol Myers Squibb. If you missed any part of this discussion visit ReachMD.com/IndustryFeatures, where you can Be Part of the Knowledge.

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