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Exploring the Significant Presence of Anemia in Myelofibrosis

Announcer Introduction:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by GSK. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Welcome to *Project Oncology* on ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me to discuss the high prevalence and impacts of anemia in myelofibrosis is Dr. Douglas Tremblay. He's an Assistant Professor of Medicine at the Icahn School of Medicine at Mount Sinai. Dr. Tremblay, thank you so much for being here today.

Dr. Tremblay:
It's a pleasure. Thank you so much.

Dr. Caudle:
To get us started, Dr. Tremblay, what role does myelofibrosis have in the high prevalence of anemia? And what are the underlying mechanisms?

Dr. Tremblay:
Sure. So the prevalence of anemia in myelofibrosis really depends on what point in the treatment algorithm you are in. So prevalence of anemia is higher as the disease progresses, as myelofibrosis is generally considered progressive bone marrow failure state. So early on in the disease, the prevalence of anemia is around 25 percent for severe anemia, which severe anemia I'll define as a hemoglobin that is less than eight, and that's really used because that really dictates which patients require red blood cell transfusion. So about 25 percent in newly diagnosed patients will be red blood cell transfusion dependent. In moderate anemia, which is a hemoglobin between eight and 10, is another 15 percent of patients.

And the mechanisms behind anemia in myelofibrosis are multifactorial. As the disease progresses and even at the beginning, there's replacement of normal hematopoietic tissue with fibrosis, which is a pathologic feature of the disease. And there's also extramedullary hematopoiesis, which manifests as splenomegaly and occasionally hepatomegaly. And at extramedullary sites of hematopoiesis, there's ineffective erythropoiesis, so inability to make enough red blood cells at these extramedullary sites. In addition, splenomegaly can cause sequestration of red blood cells. So a larger spleen can cause more red blood cells to be trapped in there, and that can lower the hemoglobin levels. And then there's also the inflammatory milieu of the bone marrow microenvironment in myelofibrosis that can dampen hematopoiesis.

And finally, treatments itself. So treatments of the disease can cause anemia as well. And you can really see this by the increased prevalence of anemia whenever someone's treated with the prototypical JAK inhibitors, and specifically ruxolitinib, where you can get a drop in hemoglobin there. Given that the EpoR receptor is actually JAK/STAT dependent, so it's really almost an on-target effect, but treatments themselves can cause anemia as well. So there's many different causes to having anemia in myelofibrosis, and those causes become even more important as the disease progresses.

Dr. Caudle:
Now if we turn our attention to its diagnosis, what are some challenges we might encounter here?

Dr. Tremblay:
Yeah, this is really challenging because the cause of anemia in myelofibrosis is multifactorial and trying to understand the different contributions is really challenging. I think an important feature is to rule out other more common causes for anemia. And it's important to identify concurrent nutritional deficiencies, for instance, and screen patients for iron deficiency, as these can be relatively easy to correct

and may prevent you from going down the rabbit hole for different diagnostic tests to try to understand.

One very important lesson though is that it is very important to measure the erythropoietin level in patients who have myelofibrosis. That can give you a sense if endogenous erythropoietin is being produced enough to really support erythropoiesis in these patients. And this can have therapeutic implications, as well as patients who have a low endogenous erythropoietin level are more likely to respond to erythropoietin-stimulating agents, while patients who have a very elevated erythropoietin level are unlikely to respond to those agents.

But I think one of the biggest challenges for assessing anemia and diagnosing and really treating anemia in myelofibrosis is trying to tease out what symptoms are related to anemia and what symptoms are related to the myelofibrosis itself. So the biggest example is fatigue. Really debilitating fatigue can be a symptom of myelofibrosis, but it also can be a symptom of anemia itself, and trying to tease out which one is contributing can be very challenging. And I share this to say that, frequently when you treat myelofibrosis with a JAK inhibitor, the anemia may actually get worse, the hemoglobin will go down, but a patient's energy level will increase. And so it really shows you that there's a disconnect between the cytokine-mediated fatigue that is due to the inflammatory condition of myelofibrosis and the fatigue that's caused from having a low hemoglobin. I find that very challenging to tease out. And really requires a trial of treatment to see if the fatigue is improved when you start to handle the cytokine milieu of myelofibrosis.

Dr. Caudle:
And how does all of this impact a patient's quality of life?

Dr. Tremblay:
Yeah, it can be a major component that really is a detriment to a patient's quality of life. And anemia itself, and the symptoms of anemia, like fatigue, can really decrease a patient's quality of life. And this has been shown independent of different factors as well to be a significant detriment to quality of life in myelofibrosis patients, just the presence of anemia.

Anemia itself is a high-risk feature of the disease. And so it can prompt you to go through different therapeutic avenues that are more aggressive and can impact quality of life. But I think the biggest impact on quality of life with anemia in myelofibrosis is transfusions and transfusion burden. And frequently, this is a major shift in the life of the myelofibrosis patients when they are able to be managed with intermittent visits, maybe every few weeks or months or so, and taking oral medications to now being required to need red blood cell transfusions to have any quality of life or even to stay alive. And patients can require red blood cell transfusions frequently, even every week or every other week. That can really put a major cost benefit or cost to a patient's well-being because they're really tied to an infusion chair, inability to take longer trips, feeling that they need to be there all the time. And not to mention the timing and cost it takes to come to an infusion center and go through that process. Even at academic centers like my own, a red blood cell transfusion can take four or five hours from start to finish with getting the type and screen to finding the matched blood to administering the blood and monitoring. And so that can be a huge detriment on a patient's quality of life.

Dr. Caudle:
For those of you who are just tuning in, you're listening to *Project Oncology* on ReachMD. I'm your host, Dr. Jennifer Caudle, and I'm speaking with Dr. Douglas Tremblay about the impact and prevalence of anemia in myelofibrosis.

Now given the effects you just discussed, Dr. Tremblay, what steps can we take to ensure we're able to make an accurate and timely diagnosis?

Dr. Tremblay:
Well, diagnosing anemia isn't, itself, that challenging; it can be done with a simple CBC. But I think it's really important to use this as an opportunity to enforce that act of monitoring patients with myelofibrosis is very important. This is not a disease where you can say, 'You have myelofibrosis, see me in six months or a year,' this is something that even in between clinic visits, I'll have patients have their blood checked regularly to see if hemoglobin is reducing over time. And it's really important to monitor that, particularly when therapies are being started, as that can affect the hemoglobin level and sometimes turn a patient who has a slightly low or normal hemoglobin further down that requires red blood cell transfusion. So it's very important to think about this and to monitor patients carefully, particularly while they're getting treatment.

We already discussed some of the other kinds of evaluations that are really important to understanding not just the cause of anemia but also some therapies as well. And that's really important that measuring things like nutritional deficiencies, iron deficiency, as well as erythropoietin level is really key to make an accurate diagnosis of exactly what can be done about this. What's causing these patient's anemia and what can be done about it?

Dr. Caudle:
And then can you tell us about some therapeutic strategies we can use to better manage anemia in myelofibrosis?

Dr. Tremblay:
Right. So unfortunately, there's a paucity of really great therapies in myelofibrosis to improve anemia. Erythropoietin-stimulating agents are probably the one that come to mind. And data is really borrowed from the MDS subsets but also data dedicated from myelofibrosis patients, showing that if you have a low erythropoietin level, guidelines say 500 or below, but in reality, myelofibrosis studies have also shown less than 125; those are patients who may actually respond to the erythropoietin supplementation with erythropoietin-stimulating agent. If you do have a high erythropoietin level, particularly above 500, but even above 125, the administration of endogenous EPO is not going to really result in improvement, so that can be challenging.

There's other treatments that we have trialed, including danazol, which is a synthetic androgen, which has been used to improve both hemoglobin and platelet counts in a variety of hematologic disorders. In transfusion-dependent patients, maybe about 20 percent will respond, but it does have some notable toxicities, including increasing PSA levels and in men with myelofibrosis, as well as some hepatic toxicity that make it not exactly ideal for most patients.

The other options include immunomodulatory agents, like lenalidomide or thalidomide, which are also associated with maybe about 20 percent response rates but have some also toxicities, including some hematologic toxicities as well.

Luspatercept is an agent that is being currently studied in this arena, particularly in combination with ruxolitinib. And this is a drug that is approved for MDS, and it's been used off-label in myelofibrosis patients, particularly with concurrent ruxolitinib. And it has a response rate of maybe about 30 percent, although this is being formally evaluated in a phase 3 trial now. And it's perhaps better in patients who have certain mutations that will predict response, such as SF3B1, or patients who have an MDS/MPN overlap syndrome with ringed sideroblasts are particularly responsive. So that's something that's coming down the pipe as well.

And the final one is momelotinib, which is a JAK inhibitor that also has activity against ACVR1, which this mechanism of action allows for more iron availability for erythropoiesis. And this has been studied in a number of different trials. And I think its ability to improve anemia is latest shown in the MOMENTUM study, which showed maybe about 25 percent of patients who were transfusion dependent will become transfusion independent, which is really great, and a higher anemia response rate, a higher improvement of hemoglobin in the patients who don't have baseline transfusion dependence. Momelotinib is a great option to address anemia in patients with myelofibrosis because it both can improve the hemoglobin count, but it's also a JAK inhibitor where you get benefits in terms of spleen size reduction and improvements in symptom burden that you would get with other JAK inhibitors, but it doesn't have as much of a toxicity, and perhaps some benefit in patients who are anemic. So this is one that's really come to the forefront of myelofibrosis treatments with anemia and is now approved for that indication.

Dr. Caudle:
Before we end our discussion today, Dr. Tremblay, what kind of impact could a timely diagnosis and treatment approach have on patient's symptoms and outcomes?

Dr. Tremblay:
It's a great question. I think a timely diagnosis of myelofibrosis and a timely recognition of anemia is really important now that we have multiple JAK inhibitors to choose from. Before we really only had one option, or more recently two or three options, but now that we have four options, I think understanding the patient's hematologic profile at baseline or even after treatment can help you design the optimal treatment for them. And this is particularly important because you really want to delay the time where a patient will need red blood cell transfusions. And ultimately, many patients will need red blood cell transfusions in the future. But if you can delay the time to needing red blood cell transfusions that can really improve quality of life. It really keeps patients feeling more like people and less like patients where they're tied up to the infusion chair all the time.

I think it's also important for timely diagnosis and recognition of anemia for considerations of other treatments, including bone marrow transplant, which if you look at the risk scores and the ways we can triage patients to transplant in myelofibrosis, being anemic is one of the strongest and most potent predictors of poor outcomes in myelofibrosis. So identifying patients who have myelofibrosis and anemia can preferentially triage those patients to transplant, which is currently the only curative therapy for myelofibrosis. So I think it's really important to not only be able to diagnose them with myelofibrosis but also understand how their hematologic profile can really guide their future therapies.

Dr. Caudle:
Well, considering the implications from our conversation today, I'd like to thank my guest, Dr. Douglas Tremblay, for joining me to discuss these diagnosis and treatment strategies for anemia in myelofibrosis. Dr. Tremblay, it was great having you on the program.

Dr. Tremblay:
Thank you. It was a real pleasure being here.

Announcer Close:
This episode of *Project Oncology* was sponsored by GSK. To access this and other episodes in our series, visit Project Oncology on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!

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