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Navigating Myelofibrosis Treatment Complexities to Optimize Care

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:
This is *Project Oncology* on ReachMD, and I'm your host, Dr. Jennifer Caudle. Joining me to share some helpful insights into the myelofibrosis treatment paradigm 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 my pleasure. Thank you so much for having me.

Dr. Caudle:
Let's start with some background, Dr. Tremblay. Can you tell us about the prevalence of different conditions of myelofibrosis, like anemia and thrombocytopenia?

Dr. Tremblay:
So there's two big lessons here I would like to convey. One is that myelofibrosis is a very heterogeneous disease and different hematologic manifestations, like anemia and thrombocytopenia, are variable based on the patients themselves. I've never met two patients with myelofibrosis who had the same sort of disease. And the prevalence of anemia and thrombocytopenia in particular, really depends on at what point of the disease you're looking at, either in the newly diagnosed setting or after someone's been treated with a JAK inhibitor, for instance.

So in patients who are newly diagnosed, the prevalence of severe anemia, which is a hemoglobin less than eight, is around 25 percent, and another 15 percent who have a hemoglobin between eight to 10. So about 40 percent of patients will have some degree of anemia less than hemoglobin of 10, and 25 percent of patients will have a hemoglobin that's less than eight and likely requires red blood cell transfusion support.

In terms of thrombocytopenia, that's severe thrombocytopenia, a platelet count less than 25 is present in about 10 to 15 percent of patients. In moderate thrombocytopenia, a platelet count of 50 to 100 is again present in about 10 to 15 percent of patients. So again, 20 to 30 percent of patients will have a platelet count of less than 100,000 at baseline. So that's all in patients who are newly diagnosed, haven't been treated yet. How about patients later on in the disease? And those numbers go up as the disease progresses, as myelofibrosis eventually resembles a bone marrow failure state where you have very significant cytopenias.

And also, the treatments themselves can cause cytopenia. So if you look at patients who have stopped ruxolitinib therapy, the prevalence of severe anemia is now 40 percent. So it goes up from 25 percent who are red blood cell transfusion dependent, all the way up to 40 percent. And if you look at severe thrombocytopenia, platelet count less than 50,000, that goes from about 10 to 15 percent in the first line versus after ruxolitinib treatment, 25 to 30 percent. And moderate thrombocytopenia is again 20 to 25 percent of patients. So the prevalence and the severity of both anemia and thrombocytopenia really increase as the disease progresses, especially after initial treatment.

Dr. Caudle:
And how do these affect the overall disease course of myelofibrosis?

Dr. Tremblay:

Right. So both anemia and thrombocytopenia are poor prognostic markers and predict for inferior survival in myelofibrosis compared to patients who don't have them. In particular, red blood cell transfusion dependency is really a potent predictor for poor outcomes in myelofibrosis and is associated with a significant decrease in quality of life.

If you look at all of the different scoring systems we have in myelofibrosis, the DIPSS score, the MIPSS70 score, the MYSEC-PM score, anemia is really heavily featured in many of them, thrombocytopenia as well.

I also would like to highlight that anemia and thrombocytopenia complicate treatment options. Many treatments that we give, especially before the advent of newer JAK inhibitors, could not be given in patients who have severe thrombocytopenia for instance, and were given with caution with patients with anemia. Now that we have JAK inhibitors that can be given in patients who have severe anemia or severe thrombocytopenia, this has improved but it still limits treatment options because many of the treatments we have for myelofibrosis are also myelosuppressive.

The last thing I'll mention about how this affects the disease course is because it is a poor prognostic marker, anemia and thrombocytopenia can identify patients who may need to be triaged to allogeneic stem cell transplant, which is the only curative option for myelofibrosis. So if patients have severe anemia or severe thrombocytopenia and they are eligible for a transplant, those are patients who should be preferentially referred for evaluation for transplant, move on to transplant if needed because we know these are very poor prognostic markers.

Dr. Caudle:
To dive in a little further, Dr. Tremblay, what kind of impact do these conditions have on patient management?

Dr. Tremblay:
Yeah, so the anemia management in general, there's many different kinds of options that we have now, although many of them don't have satisfactory results in terms of alleviating red blood cell transfusions. I mean, the most important impact that anemia has is if you need red blood cell transfusions, it's a poor prognostic marker, and spending all that time in the infusion chair regularly can really decrease quality of life, as well as overall healthcare costs too. So it really changes the tenor of myelofibrosis treatment if you have someone who's very anemic.

Both anemia and thrombocytopenia have effect options in terms of treatments for splenomegaly and symptoms, specifically JAK inhibitor therapy. So in patients without anemia and thrombocytopenia who are newly diagnosed, ruxolitinib is a great choice for a JAK inhibitor to address splenomegaly and constitutional symptoms. However, patients who have a big spleen or have constitutional symptoms are anemic, ruxolitinib may not be the best option, and now we have momelotinib, which may be a better option for those patients. In addition, if patients who have severe thrombocytopenia, platelets less than 50, or even less than 75, pacritinib, another JAK inhibitor, may be a good option for patients to address their spleen and symptoms that can be safely given in patients who have thrombocytopenia. So the prevalence in these different cytopenias impact treatment managements, as we discussed, and it's important to also address how to manage those cytopenias themselves.

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 of various conditions on myelofibrosis and patient management.

So now that we have a better understanding of myelofibrosis and some of its challenges, Dr. Tremblay, let's zero in on its treatment. What therapies are currently available?

Dr. Tremblay:
So I think it's important to really discuss addressing the anemia as one aspect of it, as well as addressing the spleen and symptom aspect of myelofibrosis. In terms of addressing anemia, there are several options. One is erythropoietin-stimulating agents, which will be familiar to many of the hematologists in the audience, as this is a drug that we're used to giving in many different disease states. And it really is most useful in patients who have a low endogenous erythropoietin level, an erythropoietin level less than 500, or in many myelofibrosis studies less than 125. Those are patients who are most likely to respond to an erythropoietin-stimulating agent, as they have an inadequate endogenous EPO level. Danazol, a synthetic androgen, is another option, which has been used in hematology for decades and can induce a transfusion independence and about 20 percent of patients with transfusion-dependent myelofibrosis, although has some notable toxicities as well.

Luspatercept, the activin ligand trap, is approved for MDS and is being tested in phase 3 studies for myelofibrosis in combination with a JAK inhibitor, ruxolitinib. And this is an agent that is probably best used with combination therapy and are based on phase 2 testing is associated with a response rate in transfusion-dependent patients of about 30 percent. And this is maybe, perhaps, better in patients who have a concurrent SF3B1 mutation, or maybe an MDS/MPN overlap syndrome as well.

And then there's momelotinib, which is a drug that can be used to both address symptom and spleen issues because it's a JAK inhibitor, but also as an ACVR1 inhibitor may allow for some improvements in hemoglobin as well. And this has been evaluated in several studies and it shows maybe about 25 percent of patients who are transfusion dependent will then convert to transfusion independence. And even more patients, a higher immune response in patients who don't have baseline transfusion dependence.

In terms of addressing thrombocytopenia, there are really few, if any, therapies that can improve platelet counts in myelofibrosis, unfortunately. Specifically, TPO mimetic therapy, like eltrombopag and romiplostim, should really be avoided in myelofibrosis patients for several reasons. It's already endogenously overexpressed in myelofibrosis, it can lead to bone marrow fibrosis in many patients, and even maybe, likely, deep vein thrombosis in some patients. So TPO agonists should really be avoided in patients with myelofibrosis to improve thrombocytopenia.

Dr. Caudle:
And what should we take into consideration when selecting a treatment for each patient?

Dr. Tremblay:
I think if you really look at guidelines, and how I practice too, it's really important to identify if there's concurrent symptomatic splenomegaly or constitutional symptoms because that will help you decide a JAK inhibitor versus no JAK inhibitor. If those are present, a lot of consideration should be given to momelotinib because this is a preferred agent because it is treating both the JAK inhibitor aspects that can address symptomatic splenomegaly and constitutional symptoms, but it also can improve hemoglobin and in some patients as well. Pacritinib, as I mentioned, is another option, particularly in patients who have concurrent thrombocytopenia and anemia.

Patients who don't have either of those, don't have symptomatic splenomegaly or constitutional symptoms, then we're really looking at things like danazol, luspatercept, erythropoietin-stimulating agents in appropriate patients with a lower endogenous EPO level and thinking about which one of those. And you have to cycle through and try different ones to see if any of them can induce any lasting response.

Dr. Caudle:
Unfortunately, we're almost out of time for today, but before we close, could you leave our audience with some helpful tips for implementing these treatment strategies into practice?

Dr. Tremblay:
Yeah, sure. So a few tips that I think are important to review. One is it's really important to rule out other nutritional deficiencies in someone with myelofibrosis and anemia because those can be easily corrected and may not require more intensive interventions. Another is to check the erythropoietin level before determining how to improve someone's hemoglobin level because that may identify patients who are likely to respond to erythropoietin-stimulating agents.

In patients who have constitutional symptoms that you think are related to myelofibrosis or symptomatic splenomegaly, JAK inhibitors are part of the treatment algorithm there, specifically momelotinib in patients who are anemic. And similarly, in those patients who have symptom or spleen burden, consider pacritinib in patients who have thrombocytopenia.

But I think it's also important to refer for clinical trial in patients who have anemia or thrombocytopenia, as those are patients who we still have inadequate therapies for and we're trying to investigate new drugs to try to improve the not only the cytopenias but also the myelofibrosis aspects as well. And also to consider bone marrow transplant referral in patients who are young and fit, who have anemia or thrombocytopenia, as these are really poor prognostic markers, and those patients should be preferentially triaged towards transplant.

Dr. Caudle:
With those strategies in mind, I'd like to thank my guest, Dr. Douglas Tremblay, for joining me to discuss treatments for myelofibrosis and how we can optimize patient care. Dr. Tremblay, it was great having you on the program.

Dr. Tremblay:
Thank you so much. Really appreciate it.

Announcer Close:
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