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Alleviating Anemia in Myelofibrosis: New Therapeutic Avenues

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is brought to you by Glaxo Smith Kline. And now, here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me to discuss the far-reaching effects of anemia on patients with myelofibrosis is Dr. Prithviraj Bose. Dr. Bose is a Professor in the Department of Leukemia at the University of Texas MD Anderson Cancer Center in Houston. Dr. Bose, welcome to the program.

Dr. Bose:
Thank you for having me.

Dr. Turck:
Well, to start us off, Dr. Bose, what are the symptoms of anemia in particular that we should be on the lookout for in patients with myelofibrosis?

Dr. Bose:
I think, by far, the most common symptom of anemia, perhaps across the board, and certainly, in our MF patients, is fatigue. And fatigue may sound a little bit trivial at times, but it can be very serious and very disabling in some patients. So just yesterday, I spoke to two patients who were really bitterly complaining about how bad their quality of life is because of this fatigue. Both have myelofibrosis. And the fatigue can be to a point where it does not permit them to do what they enjoy or partake in their daily activities. They need to rest after every little thing, so it can be really disabling.

So I think fatigue is far and away, number one, although I'd like to point out that anemia is not the only cause of fatigue in MF. I think that's just good to keep at the back of one's mind, that you could be fatigued with MF, even if your hemoglobin is 12. So there are causes of fatigue in MF that go beyond anemia, but anemia certainly is a very major cause of fatigue. And then beyond fatigue, there's things like shortness of breath and chest pain—especially if one has coronary artery disease—and then things like lightheadedness and dizziness. All of these things could be symptoms of anemia.

And the other thing that I've really noticed over the years is that the tolerance of anemia can be dramatically different between patients with MF. We tend to not consider hemoglobin over 10 as being a big deal or much of a problem, but there are patients in whom that level is too low for their functionality and their quality of life, and they can be quite impaired at that level. But conversely, you can also see patients with hemoglobin in the sixes and sevens who are not feeling it at all because they've started to acclimatize and adapt to it. But again, I think fatigue is by far the most important symptom of anemia, is very prevalent in our patients, and can really be debilitating.

Dr. Turck:
Now, what could you tell us about the relationship between anemia severity and myelofibrosis progression?

Dr. Bose:
So what we know about anemia severity and MF prognosis—let's say you break it down. Is the hemoglobin over 12, or is it 10 to 12, or is it 8 to 10, or is it less than 8? You can break it down, and there's a clear separation of survival. And also, the prognostic models all include anemia. In fact, anemia gets 2 points on the DIPS scale, for example, with everything else getting 1 point. And that tells you that

if you weigh the different factors when you compute these hazard ratios and decide how much you're going to weigh the different variables, anemia gets a high rate.

It gets a 2 on the DIPS, and every other factor gets a 1. So anemia is a part of every single prognostic model, except one called GIPS, which is purely genomic and has no clinical variables. But with any model that is based on clinical variables, anemia has a very central role there. And like I said, the worse the anemia, the worse the survival.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Prithviraj Bose about how anemia can impact patients with myelofibrosis.

So Dr. Bose, if we zero in on the management of myelofibrosis, how can the presence of anemia influence our treatment decisions?

Dr. Bose:
It very much can. So for quite a while, we've been in the ruxolitinib era so-to-speak, where ruxolitinib, which was approved in 2011 as a JAK1 and JAK2 inhibitor, really became the cornerstone of our management of myelofibrosis, and with good reason. It's a great drug in terms of shrinking the spleen, making symptoms better, and actually extending people's lives. However, it causes anemia. And this is not a trivial problem—it causes a significant drop in hemoglobin, and that does correct itself to some extent, but not the whole way.

This has a number of implications. So one, of course, as we've said, is it's not good to be anemic. It has impacts on symptoms, quality of life, burden on the healthcare system, etcetera. But also, it compromises the ability to deliver ruxolitinib. So anemia is actually the most common reason for discontinuing ruxolitinib, which is highly unfortunate because it is a good drug and it has a survival advantage in myelofibrosis. But if you cannot give it, then obviously, you're not achieving your goal. So it leads to ruxolitinib discontinuation,it leads to ruxolitinib dose reduction, and we know that ruxolitinib is a highly dose-dependent drug. Traditionally, we've tried anemia-supporting agents, like danazol or EPO, erythropoietin and its analogues, luspatercept. We add them on to ruxolitinib—that's the JAK inhibitor we are using—to try and counteract some of this anemia. But now, we have momelotinib.

So we've had momelotinib over the last about 15 months now. This is a JAK1, JAK2 inhibitor like ruxolitinib, which improves anemia. Which not only does not cause it, but improves it. And in fact, if you look at the SIMPLIFY-1 study, it is really striking how, when those patients crossed over from ruxolitinib to momelotinib after 24 weeks, you saw this really sharp rise in hemoglobin because one, the rux is gone, and two, momelotinib's benefits on anemia kick in. So now, we have a JAK inhibitor that improves anemia. So that certainly simplifies things quite a bit and adds a very valuable new tool to our arsenal.

Dr. Turck:
And what do we know about survival rates in patients with myelofibrosis who have anemia?

Dr. Bose:
Anemia is an important negative prognostic factor. It adversely impacts survival. This has been shown in multiple studies. It is included in every single prognostic model for myelofibrosis as a negative factor. And we know that the worse the anemia, the worse the survival. We know that transfusion requirement imparts an even worse prognosis on top of what anemia does. So all these things tell us that anemia is bad for you as a myelofibrosis patient. And one thing that I haven't touched on before that I'm going to touch on now, is that there is this study of ruxolitinib for six months, and they're looking at what happens to people, and the predictors of outcomes, after six months on ruxolitinib. And this is called the RR6 model, published about two years ago. And this showed some things which really underscore some of the points I made, which are that if you continue to require transfusions on ruxolitinib, and if you're not able to deliver a good dose of ruxolitinib—so anything less than 20 milligrams twice a day, which would be difficult if you are anemic—then your survival is shortened. So requiring transfusions on ruxolitinib and not being able to get a good solid dose of ruxolitinib are directly tied to a worse outcome. So that tells you that anemia in many ways really impacts prognosis.

Dr. Turck:
So with all these concerning effects in mind, Dr. Bose, in patients with myelofibrosis, how can we prioritize anemia management to improve outcomes?

Dr. Bose:
Well, I think that anemia should be as important as anything else. I think for a long time, in the field, we have perhaps prioritized the spleen and wanted to see the best possible spleen shrinkage. And that's not wrong because there are studies that show that in the context of ruxolitinib use in particular, the better the spleen response, the better the survival. So certainly, that's not a wrong approach, but I think the problem is that, in trying to obtain that excellent spleen response, you end up causing a lot of anemia. There are two ways of dealing with this. One is, we use some of these adjunct agents to counteract some of that anemia, be it an ESA or danazol or

luspatercept, and try to maintain a high dose intensity of ruxolitinib. But this is much easier said than done because the anemia supportive agents are not that great in general, and it is hard to still deliver, in many patients, to deliver a high dose of ruxolitinib that you would want and hope to have for that optimal spleen response.

So the other alternative is momelotinib. We now have this drug. It's been 15 months on the market, so people are getting more and more used to it. And this is a drug that clearly has an anemia benefit. Not only does it not cause it, but it has an anemia benefit. So I think that given it is able to address spleen and symptoms and anemia, I think it's a very attractive drug. Now, there are differences between ruxolitinib and momelotinib, and one has to get into the weeds of the data from different trials. But again, it has been compared to ruxolitinib head-to-head. It was equally efficacious for the spleen. It was not as efficacious for symptoms in that particular comparison, although in a second-line trial, it was actually more efficacious. So two large Phase 3 trials were giving us results in different directions as far as symptoms. And then there is this anemia benefit that has been seen uniformly in every single trial of momelotinib. So I think now we finally have better tools to address the anemia.

Dr. Turck:
Well, with those key considerations in mind, I want to thank my guest, Dr. Prithviraj Bose, for joining me to discuss the impacts of anemia on patients with myelofibrosis. Dr. Bose, it was great having you on the program.

Dr. Bose:
Thank you. I enjoyed it as well.

Announcer:
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