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Understanding Anemia in Myelofibrosis: Multifactorial Origins and Management Strategies

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:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss the pathogenesis of anemia in 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, thanks for being here today.

Dr. Bose:
Thank you for having me.

Dr. Turck:
Well, to start us off, Dr. Bose, what are the primary mechanisms that drive anemia development in patients with myelofibrosis?

Dr. Bose:
So this is a really important question, because it does not have to do with the disease itself. One has to look at quite a few different things. One has to always rule out things like bleeding and nutritional deficiencies. Those are just good internal medicine practices, right? As we should always do when we are investigating anemia in a myelofibrosis setting, we should not forget that it could be those other things that can happen to anyone.

But then from a disease perspective, what are the causes of MF that lead to anemia? And those are also multiple. It's not just one thing. So you can have progressive bone marrow failure, which is a classic feature of this disease. As MF progresses, it gets worse; the bone marrow simply doesn't produce red cells as well, so certainly that. Hypersplenism, because the spleen enlargement is almost a hallmark of this disease—not literally, because not everyone has to have it—but it's a very high proportion of patients that have splenomegaly. And splenomegaly causes hypersplenism, destruction of red blood cells in the spleen. And so that's another very important cause. Now, there can be some hemolysis in the bone marrow. Some of this ineffective erythropoiesis happens in MDS and in MF. You can see hemolysis within the bone marrow, leading to some of the anemia.

And then, really importantly, the effects of JAK inhibition. So for many years, ruxolitinib has been the standard of care in myelofibrosis, and fedratinib came five years ago. Now these two in particular do cause high rates of anemia, just through on-target JAK2 inhibition. So that is another major cause.

Dr. Turck:
And how might cytokine dysregulation and inflammatory processes exacerbate anemia in these patients?

Dr. Bose:
So cytokine dysregulation is critical in myelofibrosis because we know that this is a disease of inflammation, which is a key hallmark of myelofibrosis, this whole inflammatory milieu. And we know that many cytokines are elevated in these patients. Some of these have been implicated in worse survival, such as IL-8, IL-12, IL-15, and IL-2 receptor. There's been several that have actually been implicated in worse survival. But then there are others that are elevated: TGF beta, TNF alpha, CRP. You just have a lot of inflammation going on in these patients. And IL-6 is an example where that is elevated, which contributes to inflammation. And there are actually some

emerging signs that blocking that IL-6 pathway, or the signaling downstream of it, could help alleviate some of the anemia.

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 the pathogenic mechanisms contributing to anemia in patients with myelofibrosis.

Now, you started to go into each of these just before, but I was wondering if you could go into a little bit more detail about the kinds of roles that splenic sequestration and nutritional deficiencies play in exacerbating anemia in myelofibrosis patients?

Dr. Bose:
The splenic sequestration is perhaps more intuitive in the sense that we all know that this is a disease where we see big spleens and which is generally associated with hypersplenism, which is really another term, frankly, for splenic sequestration. So that certainly is going to contribute; those red cells get destroyed in these enlarged spleens.

But I think what is worth emphasizing, and I'm glad you bring this up, is that the nutritional deficiencies can actually be exacerbated by having MF. So obviously, anybody can have a nutritional deficiency, but I think more so our patients with MF can because there is an element of cachexia, right? So there is this wasting and there is a lack of appetite, so you can compound the problem through nutritional deficiencies.

Dr. Turck:
So, Dr. Bose, if we switch gears a bit and focus on factors related to patient management, how might treatment-related effects on erythropoiesis contribute to anemia?

Dr. Bose:
So since its approval in 2011, ruxolitinib has really become, I will say, the most used drug—certainly a standard of care in myelofibrosis. It has brought enormous benefits to patients with regards to spleen and symptom improvement and has improved survival. But it causes anemia. And this is not a trivial problem. Fedratinib has the same problem; it's also a potent JAK2 inhibitor, and it causes high rates of anemia.

Dr. Turck:
Now, with those potential impacts in mind, how can we leverage our understanding of anemia's pathogenesis to ensure optimal patient management?

Dr. Bose:
Hepcidin is a hormone produced by the liver, which classically is elevated in people with anemia of chronic disease, which, as you know, is also known as anemia of inflammation, right? So anemia of inflammation, or anemia of chronic disease, is something we see in many chronic diseases—say rheumatoid arthritis as an example. So hepcidin is actually elevated in patients with myelofibrosis. This has been well demonstrated. And the thinking is that some of that anemia of chronic disease type pathophysiology is also at play in myelofibrosis because when you have high hepcidin, that's going to sequester the iron in the reticular endothelial system and not permit the iron to be used for erythropoiesis. So we have that as an additional problem beyond what we talked about in a marrow failure, splenomegaly, hypersplenism, and JAK inhibition—all those things are obviously major players. But so is the fact that the iron is not free for erythropoiesis.

So in terms of leveraging that biology to improve anemia in our patients, we now have momelotinib. Momelotinib, in addition to being a JAK1 and JAK2 inhibitor, is also an inhibitor of hepcidin production, so it blocks something called ACVR1, also called ALK-2. And if you do that, you downregulate hepcidin, so the liver is making less hepcidin. And because of that, the iron is less sequestered in the reticular endothelial system, and more of it is free to enable erythropoiesis. So this is a nice new tool in our armamentarium where you're getting JAK inhibition. So you're getting your conventional benefits on spleen and symptoms, but you are not causing anemia, and you are actually improving anemia.

Dr. Turck:
Well, as those key insights bring us to the end of our program, I want to thank my guest, Dr. Prithviraj Bose, for joining me to discuss the mechanisms behind and multifactorial origins of anemia in myelofibrosis. Dr. Bose, it was great having you on the program.

Dr. Bose:
Thank you.

Announcer:
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