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Overcoming Clinical Inertia to Individualize Myelofibrosis Treatment

Dr. May:

Welcome to *Project Oncology* on ReachMD. I'm Dr. Alexandria May, and joining me to discuss how we can overcome clinical inertia in myelofibrosis care and make more individualized treatment decisions is Dr. Prithviraj Bose. He's a Professor in the Department of Leukemia at the University of Texas MD Anderson Cancer Center, where he specializes in the treatment and research of myeloproliferative neoplasms, including myelofibrosis. Dr. Bose, thanks for being here today.

Dr. Bose:

Thanks for having me.

Dr. May:

So if we dive right in, Dr. Bose, how can clinical inertia present itself in the management of myelofibrosis, particularly for patients with intermediate or high-risk disease who have anemia at diagnosis or develop it over time, and why is it so important to recognize?

Dr. Bose:

I think there are two aspects I want to touch on. So one is this whole watch-and-wait paradigm, which I really think can do a disservice to our patients. We're just saying that, "Okay, the patient is feeling fine, so maybe I don't need to intervene." So that mindset needs to change. And now, we have tools or drugs—the JAK inhibitors are what I'm referring to—that actually not only make the disease manifestations better, but also there's some survival benefit that's been demonstrated for ruxolitinib, for example, in the frontline setting. So I think my first point regarding this inertia question would be that with all that we've learned about ruxolitinib in particular—because that's been around the longest for 15 years—we ought to treat more patients than we perhaps currently do.

There is, for example, data suggesting that the baseline spleen volume is correlated to survival. So I tend to treat whenever I encounter some splenomegaly or some symptoms; I generally do not watch. I don't use very much hydroxyurea, which really is felt to not be disease-modifying; it just primarily controls the counts. So there I do initiate JAK inhibition early. And again, just because of the nature of their approvals, the data, and their individual profiles in the early setting, when a patient is not anemic, when the spleen is perhaps not huge, and there are some symptoms but maybe not too many, I think ruxolitinib has the greatest track record there. So I think that is that part. Regarding the earlier initiation of ruxolitinib, I think there's been a lot of data that has accumulated over the years suggesting that it can be disease-modifying when you start it early. So that's one.

The other one, and equally important, is that we have a number of choices now. We have more than just one JAK inhibitor. We have ruxolitinib, fedratinib, pacritinib, and momelotinib.

Dr. May:

With all that in mind, when you're selecting first-line therapy for a patient with intermediate or high-risk myelofibrosis who already has a hemoglobin below 10 and platelets under 200, what role do factors like anemia status, comorbidities, and treatment goals play in your decision-making?

Dr. Bose:

So let's start by reminding our audience that ruxolitinib is a very dose-dependent drug, and it causes anemia and generally does not improve anemia. So these are some very important tenets to remember about this drug. It has a survival benefit, but you have to be able to give it at the optimal dose. And we've learned through multiple studies like the RR6 model and even analyses of the COMFORT trials that if you can keep them at 20 milligrams twice a day—in fact, the COMFORT trials only enrolled patients with platelets over 100,000, so you're talking 15 or 20 twice a day—and then the RR6 taught us that it's really the 20 twice a day is where you're really doing them a

favor with ruxolitinib. So this is very important to remember that when your counts are such that you cannot dose ruxolitinib the way you would want, then are you really helping them with ruxolitinib?

So what we learned at EHA last year was from some really elegant post-hoc analyses of the SIMPLIFY-1 trial. And as a quick reminder for our viewers, SIMPLIFY-1 was this large head-to-head Phase III of ruxolitinib against momelotinib. And here, momelotinib and ruxolitinib were the same for spleen. Ruxolitinib was better for symptoms, and momelotinib was better for anemia, far and away.

Now, coming to the post-hoc, they looked at the anemic patients in SIMPLIFY-1, so less than 10. That's where they cut it off. And this is in line with momelotinib's label. And when they looked at just the anemic patients, they found a very interesting efficacy signal based on the platelet count. So if you looked at the anemic patients and their platelets were less than 200, ruxolitinib was no longer better for spleen. Actually, momelotinib was quite a bit better for spleen because again—the way I interpret that—in those patients, you're not giving them the optimal ruxolitinib dose. Again, going back to the point that this is a dose-dependent drug. So when you cannot deliver 20 twice a day, you're giving a suboptimal dose, and it makes sense that momelotinib would be better.

So in the anemic subset, and when you take platelets less than 200, which is a lot of patients—200 is still a relatively robust bar—so above 200, numerically, ruxolitinib actually seemed to have an advantage for spleen, not for anemia. I mean, anemia is never going to favor ruxolitinib. But for spleen, which is kind of ruxolitinib's strength, if you will, it was numerically better above 200, but below 200, it was the opposite.

So I think what this analysis has taught us is that in an anemic patient, which is again, momelotinib's label, if the platelets are less than 200 to start with, then we really need to seriously think about this: if I'm going to give them 15 BID of ruxolitinib, is that going to get me the results I'm expecting or the long-term outcomes that I'm expecting, which are best achieved with the 20 BID? Or rather, should I give them full-dose momelotinib, which is feasible to do because it's much less myelosuppressive, it tolerates cytopenias a lot better, and it improves anemia? So I think this was a very enlightening post-hoc analysis.

Dr. May:

Absolutely. For those just tuning in, this is *Project Oncology* on ReachMD. I'm Dr. Alexandria May, and I'm speaking with Dr. Prithviraj Bose about clinical inertia in myelofibrosis care and how we can overcome it.

Now, for some additional context, the current NCCN Guidelines for Myeloproliferative Neoplasms dedicate a specific treatment algorithm to myelofibrosis-associated anemia, reinforcing that therapy selection should be reassessed throughout their treatment journey and not just at initiation. So once a patient has started treatment, Dr. Bose, what clinical indicators tell you it's time to reassess, and when anemia is deepening specifically, how long is too long before that warrants a therapy change?

Dr. Bose:

I want to again mention the RR6 model. The RR6 model looks at patients who've been on ruxolitinib for six months. And again, since ruxolitinib was approved in 2011, it's been our longest-serving JAK inhibitor. So people are used to it. People tend to start with it often. But it tells you that at six months, if you're not getting 20 twice a day of ruxolitinib—and I alluded to this in our previous question—if your spleen has not shrunk by at least 30 percent, and if you are transfusion dependent, these three things all predict a worse survival.

So I think physicians can use the RR6 model as a guide. And again, it reinforces the same principles. You do well on ruxolitinib if you can get a good dose, if you're not cytopenic, if your spleen shrinks well, and if you're not needing transfusions. These are actually fairly intuitive, but the model nicely puts it together in a formal way.

Dr. May:

In addition to those guidelines, recent real-world studies have highlighted the cost of delayed recognition of suboptimal response in myelofibrosis, including data showing that a meaningful proportion of patients continue on their therapy even after progression. As patients move through their disease course and anemia worsens or comorbidities evolve, how do those factors shape your selection of subsequent therapy, and what does waiting too long actually cost the patient?

Dr. Bose:

Counts going down are the most common manifestation of progression. I would say it's more common than spleen growing or symptoms worsening. You almost inevitably see anemia show up or worsen. Platelets go down as well.

So once you are in that phase, you're in this downward spiral where you cannot increase the dose of ruxolitinib. So you end up decreasing it and just worsening the whole situation. It's sort of a vicious cycle because you give ruxolitinib, it worsens counts, and the disease progresses. That worsens counts. Then you give a lower dose of ruxolitinib, which doesn't work as well. Maybe the spleen starts to grow and will contribute to the falling counts through hypersplenism. So all of that does not do the patient any favors.

So I think now we have all the choices, particularly momelotinib because it improves anemia very robustly and it's a JAK1 and JAK2

inhibitor, so you don't have to worry about it maybe not addressing some aspects that ruxolitinib would address because in that way, they are similar. So you can give the full dose. Again, that's a very important point. You're able to deliver 200 once a day, which is the full dose of momelotinib, mostly regardless of the hemoglobin and platelets. Of course, hemoglobin would improve. Now, platelets can drop, but it's actually safe to be given all the way down to 25.

Just being cognizant of those things that you can deliver a full-dose JAK inhibitor and get JAK1, JAK2, spleen symptoms, and anemia—anemia improvement has all these survival correlations—I think is really important to keep in mind.

Dr. May:

As we come to a close, Dr. Bose, what's the most important mindset shift you'd encourage clinicians to adopt, and what should they be doing at every patient encounter to move beyond clinical inertia and deliver more individualized patient care?

Dr. Bose:

Yeah, what I would say is, one, recognize that this is a malignancy. The median survival of MF is still around six and a half to seven years. There's a 20-25 percent chance of transformation to AML. So again, I think what is important is to recognize the seriousness of the problem, refer to transplant early when that's appropriate, and perhaps not waste precious time on observation or hydroxyurea. Like I said in the beginning, we've learned about so many benefits of JAK inhibitors, granted mostly with ruxolitinib because of its long time on the market, so we have 15 years of experience. But then equally, be cognizant that we now have all these options. We have four JAK inhibitors on the market, and particularly momelotinib with its anemia benefit is a very useful tool to have.

And also something I like to mention that I don't think gets mentioned enough is that they both have short half-lives. So this is a very practical point, but switching from ruxolitinib to momelotinib is actually very easy. There is no washout, taper, or overlap required. You literally switch the next day, or at least that's what I do, because short half-life with JAK1, JAK2, you don't get the rebound and all that.

Dr. May:

Those are great comments for us to think on as we come to the end of today's program. And I want to thank my guest, Dr. Prithviraj Bose, for joining me to discuss the importance of addressing clinical inertia and tailoring treatment strategies for patients with myelofibrosis. Dr. Bose, it was great speaking with you today.

Dr. Bose:

Thanks again.

Dr. May:

For ReachMD, I'm Dr. Alexandria May. 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.