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Optimizing Spleen Volume Response, Symptom Improvement, and Transfusion Independence

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Dr. Mascarenha:
Hi. I am John Mascarenha from the Icahn School of Medicine at Mount Sinai, New York. I'm really happy to be here with my good friend and long-standing colleague, Srdan Verstovsek from MD Anderson.

Dr. Verstovse:
Hello, John. Nice to see you. Thank you for...

Dr. Mascarenha:
Nice to see you, too. Yeah. Absolutely. Today, Srdan, we are going to be talking about something that a lot of people are asking questions about, which is, now we have three JAK inhibitors approved, potentially a fourth at the summertime, and the question really is surrounding how does one approach the management of myelofibrosis, trying to achieve spleen and symptom benefit, but also considering anemia could be an unmet need and that thrombocytopenia now may influence decision-making when treating patients with myelofibrosis? I'll hand it to you. To start with, what's your general approach when considering which JAK inhibitor you're going to use, and how are you segregating the patients?

Dr. Verstovse:
Well, of course, I would like to do the best I can right from day one. For patients that have platelets about 50, typically, I would use or control the screening symptoms, if that's the problem, I would use ruxolitinib. If the platelets are below 50, then I would use pacritinib. That's how it is approved for, and I think it's quite clear distinction between the two drugs based on a platelet number. What is more problematic is the, what to do with the anemia. There are a number of patients that are anemic and I learned from your experience in other publications that perhaps in people who are given a ruxolitinib, that would be then majority of the patients that are anemic. I may start with the lower dose of ruxolitinib instead of very high dose, per the label, and build the dose up from 10 milligrams twice a day, not to cost too much of anemia or osteopenia go from 10 to 15 to 20, 25. And either with the ruxolitinib or with the pacritinib, doesn't matter, I would add if the anemia is problematic, the anemia drug. I would measure ESA, perhaps add PROCRIT as a therapy for anemia, and danazol perhaps, and try to optimize the care with the valuable therapies as much as possible.

Dr. Mascarenha:
So Srdan, when dosing with ruxolitinib, are you limiting the dosing for anemia or do you dose through and treat through the anemia?

Dr. Verstovse:
I am cognizant of the worsening of anemia in about half of the people, that's given. But I also recognize that after about four to six months in many, there is a rebounding enable cell count. So I'm not automatically decreasing the dose. Now this is to say I do use alternative dosing regimens, so I go up from 10 to 15 to 20 to 25 during the first six months as much as I can. But you are right, it's very

important to understand that the anemia is not forever with ruxolitinib, there is a high likelihood of rebound even without those adjustments. And of course adding anemia drug on top of it may even further help.

Dr. Mascarenha:
And when assessing someone's response, what is the ideal or optimal response you're looking for in terms of spleen and symptom benefit?

Dr. Verstovse:
So right away we would like people to feel better, people may feel better within a month or two, much, much better than at the beginning. And you don't even need a big dose of ruxolitinib. And of course with pacritinib, we didn't talk much about it, but it's the same dose for everybody, 200 milligrams, twice a day. So quality of life is the number one reason why we treat, right?

I objectivize this quality of life in the questionnaire in my own clinic, I try to do that every time I see the patient to see whether I need to treat and if I treat how is it going? Then I would certainly try to avoid excessive mild suppression, but we already addressed that. And then look at the degree of spleen response, as small as possible, I would like to push that spleen down because I certainly have a very good evidence from my own practice and some publications that the smaller the spleen becomes during the first six months of therapy, the longer overall durability of the benefit. So I am after the symptoms, the spleen, less mild suppression if possible, and durability. And there is lots of evidence that durability really transfers to overall survival benefit.

Dr. Mascarenha:
And in patients where you are sort of forced to dose at lower doses, ruxolitinib, let's say because of significant cytopenia, so we're talking about like five milligrams, twice, daily. Typically, what is the satisfaction level in your hands with spleen and symptom burden reduction at that dose?

Dr. Verstovse:
No satisfaction at that dose. This is really something perhaps useful transiently. Let's say you start with 15 milligrams twice a day, the platelets dropped a lot, you go to five for a few months and then you can possibly increase to 10 and maybe even to 15. But if I am at five, I know it's not going to work. I look for alternatives because five is not going to help anything much. Maybe a little bit of a symptoms for six months maybe, but you don't have a good control of the disease and I would certainly look for a change. And in that sense, I would change to pacritinib. Pacritinib is very well versed in the secondary setting. We have got evidence of its activity, not necessarily just for patients with platelets below 50. I would use it in patients with platelets below 100. The data is very solid from studies done in the past, and even the NCCN guidelines say that in second line, pacritinib should be used regardless of the platelet number. So if I'm in a situation, like you described it, very low ruxolitinib, it's not going to work, I would change.

Dr. Mascarenha:
So, you've covered a lot of different topics that we wanted to hit on today in terms of what are the considerations when initially prescribing a JAK inhibitor, how do you gauge success with a JAK inhibitor? And then how does thrombocytopenia influence decision-making, in which I think you were clear that less than 50,000, you have this niche in which pacritinib is the only approved JAK inhibitor for that patient population. But you made the point that even in patients where you're having trouble dosing five milligrams twice daily of rux or even at higher doses, pacritinib remains an option as a second line drug. And NCCN endorse as you pointed out, irrespective of platelet count. And I guess the natural question is, we spend a lot of time now talking about the benefits and relative merits of pacritinib and ruxolitinib, but what about foretinib? Where does that fit in?

Dr. Verstovse:
Foretinib reserved for some patients in my own practice in a second setting that have a good bone marrow reserve because it's causing the same degree of anemia and thrombocytopenia as ruxolitinib. And we know that the main reason for stopping ruxolitinib, after all, is the anemia. And so I'm looking forward actually to development of momelotinib. Momelotinib has been studied in numerous different phase three studies. The last one is a comparison in a blinded way to danazol anabolic steroid in a second line setting. This is where we need it the most for a benefit on a spleen and the anemia, unlike any other drug so far. And I would expect that to be approved perhaps by next summer and if that's the case, then I would say in majority of the patients in the second line, if the anemia is a major problem, I'm not going to go to foretinib. People with platelets go to pacritinib, but the bulk would probably be momelotinib. We can perhaps even discuss momelotinib for some patients in the frontline setting that are particularly anemic and don't have much of a big spleen. That's about 10% of patients. So I think there will be the role for momelotinib in a good number of patients as well.

Dr. Mascarenha:
I think you and I would both agree that in the first line setting, ruxolitinib remains the standard of care for the majority of patients. It has over a decade of clinical use and experience. And from the trials that you led in the comfort study to today's real world experience, it remains a great first option. But there are these niches we can appreciate, low platelets, thrombocytopenia, significant anemia and

transfusion burden upfront with momelotinib. And then in the second line, I guess depending on what your goals of therapy are and what your baseline features look like at that point.

Fedratinib particularly, I found it to be a very effective drug for reducing spleen volume in the second line setting. But when you have patients and it's probably two thirds of patients that end up discontinuing for significant cytopenias, then you have these two drugs that could be used, momelotinib, particularly with its anemia benefits and pacritinib, particularly in the face of extreme thrombocytopenia. Although in reality both drugs as ACBR one inhibitors likely have some impact on anemia. I guess the natural question then at this point in the discussion is if you are looking at a second line agent, and let's say the patient has both anemia and thrombocytopenia, which often can co-occur, how does one make a decision in that setting where both cytopenias could be present.

Dr. Verstovse:
If in that particular patient the anemia is the major problem, patient is transfusion dependent, requiring transfusions all the time and doesn't have such a big problem with the spleen, that would be then the case for momelotinib. If the patient is less transfusion dependent or requiring transfusions and it's much more of about the spleen control, then possibly pacritinib would be the one.

Dr. Mascarenha:
Okay.

Dr. Verstovse:
But then they certainly overlap. I think it's a judgment call of the treating doctor.

Dr. Mascarenha:
Excellent. And maybe one last word on if you could compare the toxicity profile, the major differences in toxicity profile amongst these three or four rather JAK inhibitors.

Dr. Verstovse:
Yeah, we can unfortunately talk about fedratinib as perhaps a little bit more toxic than the other because we have a higher rate of GI rotation, nausea, vomiting, diarrhea, and you need to measure the timing level because of very distant, but it's a blood work warning, when you can follow up on this. So measuring, timing, and supplementing it. The pacritinib actually comes when you prescribe it with the anti-diarrhea medication because it can also cause some diarrhea with the proper institution of supportive care, that's not a problem. Momelotinib doesn't have much of that. It's really very well tolerated. I would say pretty safe. Ruxolitinib is, as we know, anemia, osteopenia, not much of the GI toxicity. So a little bit different toxicity profiles, but all manageable in fact.

Dr. Mascarenha:
Fantastic. So Srdan, I want to thank you for joining me today as we discuss optimizing JAK inhibitor therapy to achieve spleen and symptom benefit, maybe even anemia benefit as we move forward with new JAK inhibitors that are approved and soon to be approved. And it makes it more complex. The decision-making is a little bit more complex than it was for over a decade where it was one therapy and that was it. But that's a good problem to have and I'm glad we're having this discussion and I'm glad you joined me for this and I appreciate the audience's attention to this topic. Thanks very much.

Dr. Verstovse:
Thank you very much.

Announcer:
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