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What Are the Best Practices for Assessing and Managing Common Adverse Events With JAK Inhibitors?

Announcer:
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Dr. Verstovek:
So, we're going to discuss over next about 10 minutes the best practices in managing side effects. And there are some side effects from current JAK inhibitors, current and one that soon is to be possibly approved. There are four of them. We're going to talk about the ruxolitinib, fedratinib, pacritinib, and momelotinib.

You and I probably use in majority of the patients in a pharma setting, ruxolitinib is a backbone for what we want to do with the patients. Now, are there specific side effects that you are worried when you prescribe ruxolitinib? And how do you go about it?

Dr. Mascarenhas:
So, I think at this point most people are quite comfortable with ruxolitinib after a decade of commercial use and experience with a drug that, I would say, is really well tolerated. I mean, in the spectrum of drugs that we give in malignant hematology, this is an easy drug to deliver, a twice a day dosing.

Easy bruising, dizziness, headaches were some of the more frequent low grade complaints that were reported in the comfort studies. Sometimes I see them in patients, but often they're so low grade and they're outshined by the clinical improvements that the patient sees that they're very rarely a reason for discontinuation. I really can't remember the last person I saw who discontinued for gastrointestinal toxicity. So, from a side effect profile, it's a well-tolerated drug.

Now, there is on-target and expected myelosuppression. You get a certain degree of thrombocytopenia and anemia. It's predictable in its cadence and its kinetics. I think it's important, as you've pointed out previously, to treat through, particularly in the first several months, the anemia because it often does get better. And the thrombocytopenia is something that one needs to calculate and potentially adjust the dose, depending on how severe the curve is with the thrombocytopenia. So, you need to be aware of the myelosuppression, you need to follow the patients and track that and potentially dose adjust. But in many cases, I would say treat through and see what the next three to six months brings you, definitely before one discontinues therapy, but before one starts reducing the dose unnecessarily. So, I think those are the major initial considerations.

With ruxolitinib, there is over time probably an increased risk of infectious complications, whether it's viral, bacterial, maybe some atypical fungal infections. These are not common and for the most part are things that we could see anyway in patients, but may occur at a higher frequency. I think the shingles, which I used to see more frequently, I rarely see at this point because I have all my patients get the Shingrix vaccine and that seems to significantly reduce the occurrence of shingles. I'm not a believer that there's an increased risk of secondary primary malignancies such as lymphoma that was once a concern. I think skin cancers, squamous cell and basal cell, might be there and particularly in patients with PV that were treated with ruxolitinib that saw a lot of hydroxyurea.

So, other than skin exams and watching blood counts and managing infectious issues if they arise, it's a pretty easy drug to tolerate without a black box warning without any specific supplementation needed.

Dr. Verstovek:
Yeah, thank you very much. Excellent summary. And giving a vaccine to all the patients is quite a surprise to me. We are a little bit more selective and perhaps suggest this to older people, but it's good practice. I think it makes a lot of sense.

The skin cancer comes up occasionally. And I want to see your view. I agree in policy if the patients have better outcome, they're going to be on ruxolitinib for, I don't know, seven, 10 years on average. And maybe this is a bit more concerning in that sense of the life expectancy. But the myelofibrosis patients, this transformative effect on the skin and quality of life, to my view and knowing that the life expectancy is shorter, that issue of a skin cancer is not such a big deal. I mean, we deal with that. We don't prevent patients from benefiting from ruxolitinib or stop ruxolitinib because of appearance of a skin cancer. What's your take?

Dr. Mascarenhas:
I 100% agree with you. Skin cancer in 2022, going into 2023, is not going to affect their longevity and their duration of benefit of rux. And I have patients get yearly skin exams and address lesions that appear in a timely manner so that they don't become disfiguring. But it's really a minority of patients. And it's rarely a reason for even consideration of discontinuation. I can't remember the last time I really stopped ruxolitinib in a myelofibrosis patient who's benefiting from the drug because of the appearance of squamous cell or basal cell. So, I agree with you. In my mind, not a major concern

Dr. Verstovek:
And very shortly on fedratinib, it's not very much used and this is because of toxicities. That's my perspective here, because otherwise it's very good for the spleen and symptoms. But comparing, at least in the frontline setting, it has a GI toxicity, but two-thirds of the patients require some antinausea, antidiarrhea. You have to measure thymine because of possibility or interfering with the uptake of thymine from GI tract. So, it's mandatory to measure and supplement it if it's low. It's a little bit more complicated to give it.

But I do give it in a second line setting. And if you give an antinausea, antidiarrheal, and thymine, yeah, it's three extra pills. But if you do get that, people can have a good responding symptom in the spleen. But that's a smaller group of people actually, even in the second line. There is much more enthusiasm about pacritinib then. How can you summarize for us in a couple minutes side effects of pacritinib?

Dr. Mascarenhas:
So, pacritinib like fedratinib, is also a FLP-3 inhibitor, so there is a GI toxicity profile associated with pacritinib. In my opinion, and if you look at the data, it's mostly low grade. It occurs within the first two cycles, very easy to manage. It's about half the patients. It's rarely a reason for discontinuation. And as you pointed out, if one is prepared for the potential for some diarrhea and nausea and has an anti-emetic or antidiarrheal available, it is very easy to manage. So, I think just making sure the patient is aware that there's a potential for GI toxicity is half the battle.

The other aspect to consider with pacritinib is there may be an increased risk of bleeding tendency with pacritinib, irrespective of the depth of the thrombocytopenia. Of course, pacritinib is primarily used in patients with thrombocytopenia and thrombocytopenia often associates with bleeding. And we did see an increased frequency of epistaxis and GI bleeding.

Dr. Verstovek:
Yeah, I wanted to ask you about this because the medication was on clinical hold by FDA before approval and it was because of the bleeding. I think you need to have some EKG measurements before you give it and be careful not to combine with medications that increase the QTC. In your opinion, how important is this?

Dr. Mascarenhas:
So, when the final data analysis of safety was performed, there really wasn't a difference in cardiovascular events when comparing pacritinib to best available therapy, which also included ruxolitinib. I think the initial concern that led to the clinical hold for this toxicity concern was probably not actually a valid concern as it relates to pacritinib.

The bleeding, on the other hand, I do think there's an increased risk of bleeding. I definitely don't know why that is, whether it's a qualitative platelet effect. My recommendation when using pacritinib, and particularly since it's in low platelets to begin with, is to address underlying coagulopathies. This is not the kind of drug that you would necessarily want to give while receiving concurrent anticoagulation. And to monitor the patients for worsening thrombocytopenia and the need for dose adjustments or platelet transfusions.

But the reality is, if you look at patients with low platelets, extreme thrombocytopenia, they have a very poor prognosis. So, I think some of the safety concerns that may have even existed, whether they're even valid at this point, are often overshadowed by the fact that it's a very poor prognostic group of patients with limited to no options. And pacritinib really offers an opportunity to salvage some of these

patients.

Dr. Verstovek:
And the upcoming momelotinib, if it gets approved by next summer, it looks like it's pretty safe. What we know is that the dose intensity, that means the same dose as it was prescribed, stays on for a longer period of time. 96, 97% of the patients just enjoy it at given dose. And it can improve, to a degree, quality of life, spleen, and can also improve some anemia as well. So, I'm actually less concerned about momelotinib here. No GI, no neurological, no little bit of bleeding, nothing really stands out. It seems kind of a fair drug and good for the improvement on multiple aspects of myelofibrosis patients without much of a toxicity. Is that right?

Dr. Mascarenhas:
I mean, that's my impression as well. I mean, there was initially a concern in the early development of the drug of the potential for peripheral neuropathy, which was recorded between 10 and 12%. And there's a lot of data with momelotinib now in terms of patient exposure and years of exposure and long-term exposure and safety follow up. It does have a very, very attractive safety profile. So, not a significant signal of GI tox or, as you pointed out, neurologic or infectious toxicity. So, it would be a nice fourth drug addition to our armamentarium that doesn't bring a lot of toxicity baggage with it.

Dr. Verstovek:
Yeah, I agree with you. So, hopefully we'll get it approved. Thank you, John. It was wonderful discussion on the safety profiles of four different JAK inhibitors. I hope this was useful for our listeners and viewers. Thank you and have a good day.

Dr. Mascarenhas:
Thanks, Srdan.

Announcer:
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