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www.reachmd.com
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(866) 423-7849

Indications to Switch Therapies for Myelofibrosis Patients

Announcer Introduction
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Glaxo Smith Kline. Here's your host Dr. Charles Turck.

Dr. Turck
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Here with me today to discuss strategies for switching therapies while managing patients with Myelofibrosis are Drs. Justin Arnold and Jerry Spivak. Dr. Arnall is a Clinical Coordinator of Hematology at Atrium Health Specialty Pharmacy service in Charlotte, North Carolina. Dr. Arnall, welcome to the program.

Dr. Arnall
Hey, thank you for having me.

Dr. Turck
And Dr. Spivak serves as the Emeritus Professor in Medicine at the Johns Hopkins University School of Medicine. Dr. Spivak, thanks for being here today. So diving right in and starting with you, Dr. Arnall, what first-line and second-line therapies are available for patients with myelofibrosis?

Dr. Arnall
Yeah. So certainly a good question. In general, right now, what we have for the management of myelofibrosis are our JAK inhibitors. And so to start, what most people are probably familiar with because it's been around for the past decade is ruxolitinib. And so that has been our major or primary first-line option with manipulations downstream as needed. And then more recently, we've had the approval of multiple other JAK inhibitors, fedratinib, pacritinib, and most recently momelotinib, that actually do have data, clinical trial data and support in both the first-line and second-line following ruxolitinib data that can be considered.

Dr. Turck
Now with those therapies in mind, Dr. Spivak, how can we select the best one for each patient through the different stages of myelofibrosis?

Dr. Spivak
So the first question has to be a little different from my perspective because what's happened in the field of the NPN field with respect to myelofibrosis makes it very confusing, not only for patients but also for physicians who are not doing research in the field, and that is what's in a name. Myelofibrosis is a term we use for the change in tissue structure so that each tissue has its own structure. The bone marrow has its own unique structure, and when tissue changes, when a tissue reverts from its normal structure due to, could be anything, it could be a toxin, it could be an infection, it could be a cancer. Myelofibrosis is one of the changes that occur. And myelofibrosis is not a disease. It is a histologic change in tissue structure where there is an increase in fibrous tissue where there was no fibrous tissue before.

Importantly, myelofibrosis is not only seen in malignant diseases, like the myeloproliferative neoplasms, it's also seen in benign diseases as well. It is a reversible reaction, and it is responsive primarily to, as I mentioned, things that are toxic to the bone marrow. And since it is reversible, it itself does not impact on the ability of a bone marrow to function. Now you can argue that and say cirrhosis of the liver fibrosis, there impacts on liver function, but remarkably in the bone marrow, it's not the myelofibrosis that impacts, it's a bad stem cell. And without recognizing that, we can get in a lot of trouble because there are a lot of people who think we have to get rid of myelofibrosis. But myelofibrosis should not be the target. It should be the stem cell. That's the target. So that's the first point that has to

be made.

The second point is myelofibrosis is disease dependent. So you have three myeloproliferative disorders, essential thrombocytosis, polycythemia vera, which is the most common and primary myelofibrosis, which is the least common. And primary myelofibrosis is generally a disease of patients over the age of 60. It has a bad prognosis because it has the worst stem cell defect. Polycythemia vera patients can have myelofibrosis for as long as 40 years because I followed these patients. And it does not impact. It's when the stem cell is damaged that the bad things occur. And unfortunately, people don't read the old literature, which makes these points very clear. So the first thing you want to think about when you talk about what drugs are going to work, some drugs, probably all drugs are going to work better in myelofibrosis associated with polycythemia vera than in primary myelofibrosis where the stem cell is badly damaged.

Dr. Turck
Coming back to you, Dr. Arnall, what factors indicate that a patient may be ready to switch therapies?

Dr. Arnall
Yeah, so in general, what we're thinking about when we're considering switching therapy is either efficacy or tolerability. So nothing new necessarily there. In terms of tolerability, the major driver for consideration for switching therapy when I say major, mostly or historically, that refers to ruxolitinib tolerability, but certainly the others, the novel agents as well. We're usually considering cytopenias, anemia, thrombocytopenia being particularly problematic with our GAK inhibitors. And then other tolerability issues, gastrointestinal effects and whatnot largely come to mind. Those tend to be generally manageable are supposed to be transient but may be particularly problematic for patients.

In terms of efficacy, the outcomes that you're looking for as dictated by clinical trials would be spleen volume reduction. And so there are generally some goals there, but I would say more significantly it would be patient symptoms and issues as they pertain to their myelofibrosis. And so generally, you'll have some thresholds or you'll be monitoring a patient's symptom scores and risk stratification over time. And if those are getting consistently worse and patient is expressing that symptoms and whatnot are impacting their daily living then certainly there should be some consideration made for changing your therapeutic approach there.

Dr. Turck
For those, just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Drs. Justin Arnall and Jerry Spivak about switching therapies and the management of myelofibrosis. So, Dr. Spivak, now that we have a better understanding of when to switch a patient's therapy, how do you then work with them to ensure a timely and seamless transition?

Dr. Spivak
So you try to get the maximum mileage you can get out of a single drug. And the reason that you would switch therapy—there are three reasons—one, there's patient tolerance. Not everybody can tolerate ruxolitinib, for example. So that's one reason for switching. The second reason for switching is drug toxicity. And so what you will see in patients with you start on ruxolitinib as you'll maybe see an exacerbation of anemia, which may, if you follow carefully and you start at the standard dose that if you have to increase the dose because splenomegaly is not responding, you may see more anemia. So anemia would be one reason to switch the dose. Thrombocytopenia would be a second reason. Though we have published, and it's only in polycythemia vera, that if you nurse the patients along and actually give them platelet transfusions if they need it that those patients will actually sometimes bring their platelets count back reasonably back to normal.

So it's treating a disease like polycythemia vera. It's a marathon, not a sprint. So patient tolerance, drug effectiveness, and drug toxicity are three things that you look at in treating patients. And sometimes you can take a drug holiday and allow the bone marrow to rest and start back and you may get the same effect. But I also don't escalate rapidly. You just want to take time and see what the patient can do with the drug. Now if you have intolerance, that's one reason to switch drugs. And then the question is, which drug will you next use? And we are now fortunate that we have four drugs, ruxolitinib we know the most about, and that's the drug that every other drug should be compared to. The different drugs have different toxicities.

And so for example fedratinib was the second drug to be approved. And so that's a drug that we also have a little more experience with. ~~T~~hat drug has more GI toxicity because it has some activity against ~~uh,~~ another tyrosine kinase called FLT3. So patients sometimes don't tolerate that as well. We also have to give thiamine with it because it had the possibility of getting thymine deficiency with that drug. So we want to keep the thymine levels up and avoid neurologic problems principally.

The third drug would be Pacritinib, which also has some GI toxicity because it hits FLT3 as well. And it also has an extended effect because it hits another receptor and has been proven to increase to be used in patients whose platelet counts are below 50,000 where we usually don't like to start ruxolitinib, though. I personally would rather start with ruxolitinib and see what happens then and save pacritinib for when I may really need it. But there is an indication if platelet counts are very low, that people like to start with pacritinib

and jump over fedratinib. Now we have the most recent tyrosine kinase to be approved, and it's actually been around as long as some of the others. And that's momelitinib, which also has a wider effect on other enzymes. And it is supposed to increase if you have someone who's anemic, it is thought to improve patients who are transfusion dependent to make them independent or improve the hematocrit. And so that's one you might consider using for anemia. But I would always want to start with the ones, the tyrosine kinase like ruxolitinib and fedratinib for which we have the most experience. But we're fortunate to have all these choices.

Dr. Turck
And in addition to knowing when and how to switch therapies, Dr. Arnall, what other patient-centric strategies for myelofibrosis care do you recommend?

Dr. Arnall
So one would be your general supportive care. So what measures are being taken to address the symptoms that a patient is expressing? I think that sometimes it does get overlooked the significance and importance of using the validated and NCCN guideline-recommended, symptoms assessment scores that we're also using clinical trials. And so I think utilizing these and making sure that you're responsive either in disease modifying therapy or disease modifying versus directed therapy or in other surrounding supportive care management, I think is all particularly useful. And then beyond that, I think that our options currently, we have four options with regard to JAK inhibitors, and again, approved in both first and second-line therapy. And so potentially we have the ability there to select based on both disease and patient-specific factors. So whether that be cytopenias, which is where the conversation is and around mostly to direct the selection of these therapies or as it pertains to general tolerability that you would expect. I think that these can certainly be considered in the modern era now of myelofibrosis care.

Dr. Turck
Thank you, Dr. Arnall. And before we end today, Dr. Spivak, what kind of impact can a timely therapeutic transition have on patient outcomes?

Dr. Spivak
Well, when we first had ruxolitinib and nothing else to use, I can tell you and other people have seen the same thing that you can see remarkable effects in therapy-naive patients and patients. We've had some patients who because we couldn't control the spleen another way had gotten huge spleens. And they say, well, we're always looking for at least 50 percent of the people have a 35 percent rock reduction in splenomegaly. Well, that's fine and good in a clinical trial, but you're going to find patients who first see these drugs who may only get a 10 percent response or less, who suddenly feel so much better because these drugs suppress inflammatory cytokine production so that you get other benefits than just shrinking the spleen a certain amount. So you can get mileage out of these drugs when patients are naive to the therapy.

The time to switch, there are two things I should say. Obviously, the time to switch is if, as I mentioned, is patient intolerance, drug toxicity, or drug lack of efficacy. But at the same time, the idea I think is to go low and slow and escalate and see as if you get as much as you can out of the drug you're using before you switch to another drug. And of course, there are other therapies that we can add in with the tyrosine kinase now to hit the stem cell with different therapies so that it can't escape. If it escapes from one therapy, it may not escape from the other therapy.

Dr. Turck
And with that potential impact in mind, I want to thank my guests, Drs. Justin Arnall and Jerry Spivak, for joining me to discuss how and when we should consider switching therapies for patients with Myelofibrosis. Dr. Arnall, Dr. Spivak, it was great speaking with you both today.

Dr. Arnall
Thank you so much.

Announcer Close
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