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Factors Guiding First-Line Treatment Decisions for Myelofibrosis and Anemia

Dr. Turck:

This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me to share his insights on the key factors guiding first-line treatment decisions for patients with myelofibrosis and anemia is Dr. Douglas Tremblay. He's an Associate Professor of Medicine at the Icahn School of Medicine at Mount Sinai in New York. Dr. Tremblay, welcome to the program.

Dr. Tremblay:

Thank you so much for having me, Dr. Turck.

Dr. Turck:

Absolutely. Well, let's start with the big picture, Dr. Tremblay. When you're evaluating a newly diagnosed patient with intermediate or high-risk myelofibrosis who also presents with anemia, what clinical factors have the greatest influence on your initial treatment decisions, and where does anemia fit alongside the consideration of spleen burden, symptom severity, platelet count, overall disease risk, and molecular features?

Dr. Tremblay:

Well, this is a fantastic question to start with, and this is really a question that has evolved considerably over the last several years thanks to the availability of newer therapeutic options. So the framework has shifted from risk stratification alone, which is accomplished with multiple different risk stratification scoring systems such as DIPSS, to one where these different clinical features are really weighed together, including spleen and symptoms, but also cytopenias and anemia, as you mentioned.

Anemia is a particularly important variable to consider because baseline hemoglobin and transfusion dependence now actively steer which JAK inhibitor class to start with. But I will also mention that molecular features like high molecular risk mutations, karyotypes, or even higher-risk disease still inform not only prognosis, but also a key therapeutic decision, which is the referral to a bone marrow transplant specialist as bone marrow transplant remains the only curative therapy for myelofibrosis.

So anemia has really entered the conversation with newer JAK inhibitors, but evolving our understanding of the molecular features is also still very important.

Dr. Turck:

Now building on that, baseline anemia is often one of the defining features of these patients, as we've been discussing. So how do you determine when anemia should become the primary driver of first-line therapy selection versus one component of a broader assessment that also includes transfusion burden, disease manifestations, patient characteristics, and overall treatment goals?

Dr. Tremblay:

A key consideration anytime we're discussing therapies with patients with myelofibrosis is: what are the treatment goals here? And anemia is a really important component of that. Specifically, a key inflection point is transfusion dependence. That turns someone who may come into the clinic once every three or four months to someone who needs to be in the infusion chair once a week. So this is a really key component to consider.

Before attributing anemia to myelofibrosis itself, it's important to look into reversible causes, like iron deficiency or GI blood loss. And therapeutically, there are some tools that we can use to understand what the best treatment approach is, such as serum erythropoietin level. If that's very low, that may favor trying to add on an erythropoietin-stimulating agent. But other drugs like JAK inhibitors that have anemia benefit, like momelotinib and pacritinib, are agnostic to EPO levels, and those are useful whenever splenomegaly and symptoms

coexist with anemia. And recent guidelines now support the use of JAK inhibitors with these favorable anemia profiles as first-line therapies with anemia-directed therapies, not just after failure of a supportive agent like an erythropoietin-stimulating agent.

Dr. Turck:

Now, another factor that frequently complicates these decisions is thrombocytopenia. Would you tell us how the baseline platelet count influences your treatment selection, particularly when you're balancing the need for disease control with maintaining hematologic function and treatment intensity?

Dr. Tremblay:

So platelet count is really a factor that is considered for dosing and drug selection and not just as a side consideration. Severe thrombocytopenia, which is a platelet count below 50,000, narrows the treatment options. And only pacritinib, one of the JAK inhibitors, is specifically studied and dosed in this population. And that allows for continued JAK inhibitor therapy where others like ruxolitinib and fedratinib may need dose modulation or avoidance in general. Momelotinib can also be used in the setting of severe thrombocytopenia.

But there's a real tension there between needing JAK inhibitors to optimize spleen and symptom control versus some of the side effects that ruxolitinib and other JAK inhibitors have of worsening cytopenias. And this is really where the differentiated myelosuppressive profiles of these different drugs come into play. For severe thrombocytopenia, maybe use one that is studied in that setting like pacritinib or momelotinib, while drugs like ruxolitinib and fedratinib should be avoided in the severe thrombocytopenic patients.

Dr. Turck:

Now, patients rarely present with anemia alone. So when you're balancing symptomatic splenomegaly, constitutional symptoms, and cytopenias, how do you prioritize those competing clinical needs in first-line therapy selection for an individual patient?

Dr. Tremblay:

So it's important to, as you mentioned, individualize the patient and understand which is the most pressing issue. Some patients with myelofibrosis have almost like a bone marrow failure-type phenotype where they have very profound anemia, while others have anemia that exists in a consequence of symptomatic splenomegaly or debilitating constitutional symptoms.

Now, the use of JAK inhibitors is really targeted towards those patients who have a large spleen or have a symptom burden. And the cytopenic profile, like anemia, really determines how to give a JAK inhibitor—for instance, using momelotinib rather than whether or not to use a JAK inhibitor itself.

Now, no single agent maximizes all three domains equally, and real-world practice is really a trade-off between spleen and symptom responses versus hematologic tolerability. But this is a good example of where shared decision-making and setting expectations about which one of these axes we're going to be trying to improve is really emphasized and should be prioritized for each individual patient.

Dr. Turck:

For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Douglas Tremblay about how we can make individualized first-line treatment decisions for patients with myelofibrosis and anemia based on factors like hemoglobin levels, platelet count, and the presence of splenomegaly.

Now, if we switch gears and look beyond those key factors, Dr. Tremblay, what evidence from recent clinical trials and real-world experience has been most influential in changing the way you approach first-line treatment selection for patients with myelofibrosis and baseline anemia?

Dr. Tremblay:

Some pivotal randomized trials plus a growing amount of real-world cohort data have shown that these newer JAK inhibitors like momelotinib and pacritinib can preserve or even improve hemoglobin levels and convert some patients who are transfusion-dependent to transfusion-independent while still achieving those goals of controlling spleen and symptoms. And this has really expanded the therapeutic options for those anemic myelofibrosis patients.

Real-world data is reinforcing what we've seen in the clinical trials—these benefits exist, including in patients who may not qualify for the trial that are older or more heavily cytopenic. And overall, it emphasizes that you really need to tailor JAK inhibitor therapy based on the different hematologic profiles into creating a more phenotype-matched selection for JAK inhibitors at diagnosis.

Dr. Turck:

Now, when more than one first-line treatment may be appropriate, how do you weigh differences in efficacy, tolerability, transfusion requirements, and hematologic adverse effects to identify the best fit for an individual patient?

Dr. Tremblay:

No agent is perfect across all of these axes, and a few points I would like to make is that it's really about ranking priorities for each patient. If transfusion dependence is the biggest issue a patient has that's most bothersome to them, then something that has the best chance of getting them out of the infusion suite is something that really should be prioritized. In other patients, they may have severe symptoms from splenomegaly or have more mild anemia, and therefore, the therapy should be tailored towards those types of patients.

Now, the other point I'll make is that this isn't a contract that you sign and you have to go forward with. You can switch therapies. So if one agent is not serving a patient well, it's reasonable to try a different therapy. And these different treatment-emergent cytopenias and need for dose reduction is often a decision point to switch therapies to a different JAK inhibitor. There are other things like GI tolerability and class-specific adverse events, which go into deciding which is the first agent to try and which JAK inhibitors can be tried if that first one is not accomplishing those goals.

Dr. Turck:

Well, it's clear that no two patients with myelofibrosis and anemia present in exactly the same way. So given everything that we've discussed today, Dr. Tremblay, when you're considering factors like anemia severity, platelet count, spleen burden, symptoms, molecular features, and patient preferences, what principles guide your decision to select one first-line treatment strategy over another?

Dr. Tremblay:

No patient is univariable, and for most patients, you really have to consider the different multiple variables to incorporate into your treatment decisions. And those include hemoglobin and transfusion status, platelet count, spleen size, and the symptoms from splenomegaly, constitutional burden, molecular risk, and patient goals, and feed those all into one decision rather than being addressed sequentially.

And the other point I'll make is that first-line therapy no longer really means one default agent for all comers. Therapy should really be tailored to that specific patient's constitutional issues and the combination of all of their different problems to see which one can be used first.

Now, earlier and more individualized treatment selection rather than reactively switching after failure is really the direction the field is moving in. And thankfully, we have more agents now that can tailor the therapies to produce the best results for each individual patient.

Dr. Turck:

With those key principles in mind, I want to thank my guest, Dr. Douglas Tremblay, for joining me to discuss first-line treatment selection strategies for patients with myelofibrosis and anemia. Dr. Tremblay, it was great having you on the program.

Dr. Tremblay:

Thank you so much. I really appreciate being here, Dr. Turck.

Dr. Turck:

For ReachMD, I'm Dr. Charles Turck. 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.