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How Do I Manage a Patient With Myelofibrosis and Severe Anemia?

Announcer:
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Dr. Verstovek:
Hello, I'm Srdan Verstovsek. I'm professor of medicine in the leukemia department at MD Anderson Cancer Center in Houston, Texas. Today, I'm going to talk on the topic of how do I manage a patient with myelofibrosis and severe anemia. The treatment approach to myelofibrosis really is divided based on what bothers the patient. First. We would, as it is in on this slide, divide the patients in those that are at a high risk versus low risk for dying, and then we would refer them to a bone marrow transplant if they're high risk, that means usually a life expectancy less than five years, but less than 10% of the patients really do that.

So then we say, "What's wrong?" And we would go by the symptoms first: Are there present symptoms or not, or different types: vomiting, night sweating, low-grade fevers, itching, cachexia, fatigue, and others, and start the therapy with JAK inhibitors, more or less. That would be ruxolitinib, fedratinib, or pacritinib. Pacritinib is specifically for patients with platelets below 50. And if anemia is present, perhaps used alone or in combination with JAK inhibitors from a list of ESAs: danazol and lenalidomide, thalidomide, or even now luspatercept, which is approved for a different indication but useful in myleofibrosis patients.

So unfortunately, it's not that simple in everyday practice. Many patients have overlapping features. So what do we do when patients have symptoms in spleen and anemia? Symptoms may be spleen-related or is general systemic symptoms. And in that setting then, we have a little problem because some of the therapies will worsen the anemia. Ruxolitinib and fedratinib are very well-known to improve the spleen and symptoms but worsen the anemia in about half of the patients and the thrombopenia as well in about up to 20% of patients. Ruxolitinib being the number one choice in every practice is of particular interest because as you can see here, anemia appears to be the leading cause of Ruxolitinib discontinuations. It's affecting the delivery of optimal dose, and that's why we want to see how can we optimize the delivery by alleviating the anemia.

One way is to add another agent, and here I give a choice of luspatercept as presented on this slide from the phase two open label study. By the way, this therapy, luspatercept, is in a phase three blind randomized study, but it's already listed as effective in NCCN guidelines for anemia and use of label in some circles. What you have here is results in elimination of the transfusions or decreasing transfusions by 50%. And what is in a red square in the middle, it's the group that has the most benefits. This is the people who are on ruxolitinib by require transfusions as the main problem, and here we go. Right there in that group, we have the best response to luspatercept, and this is where the phase three study is being done.

But the major development for us is possible approval of momelotinib next summer. And momelotinib is not only JAK one, JAK two inhibitor as its in cartoon to the left, but also inhibitor of ACVR1. ACVR1 is as you see, receptor on the surface of hepatocytes and decreases hepcidin, which is regulator of iron metabolism, and that would allow more red blood cells for anemia. That particular benefit of symptoms in anemia was tested in a momentum study, which was a phase three randomized blinded study between the momelotinib

and danazol in secular setting. Everybody was exposed to ruxolitinib. Everybody had a hemoglobin less than 10, platelets above 25, and TSS, total symptom score, a quality of life of 10 points and more. Particular focus was on symptoms but also multiple measurements of anemia, and a summary is given here.

First, just to say about the symptoms, waterfalls are easy to understand, massive improvement in a quality of life in a secular setting. About 25% eliminate half of the symptoms. That is also, of course, in control of the spleen. Here, we have about 23% decrease in spleen by at least 35%, and then the most important one is improvement in the anemia judged by transfusion independence. If you look at the bars to the left, you have a blue bars; 13% of patients at the beginning were transfusion independent. After six months on momelotinib, 31%, and the gray bars are on Dana not much of a difference. And more to that point, you see to the right hemoglobin goes up, blue curve is the momelotinib-treated patients. It goes up, and that doesn't go that much up with danazol after 24 weeks. In fact, all the patients on danazol crossed over, and you see how the numbers improve. So very valuable anemia benefit of momelotinib, particularly perhaps suitable for secular setting.

And with that transfusion independence, we now have evidence that this possibly leads to longer survival. This is quite exciting. We would like to confirm that by more studies and longer follow-up because, really, it makes sense to say that by eliminating transfusion, preventing transfusion, which is better prognostic practice, people would live longer. Regardless of the transfusion independence in the patients with low platelets, momelotinib therapy appears to be improving the outcome patients by anti-inflammatory potential. So a lot more to learn about over longer period of time from momelotinib studies.

Where would then we see the momelotinib use in some patients in frontline along with pacritinib, ruxolitinib, and fedratinib on the left side, but also momelotinib for anemic patients in a second line where we still have for pacritinib for patients with low platelets, fedratinib for patients with a big spleen but normal bone marrow function, and certainly we also talk about combinations coming up in investigational arena. I thank you so much.

Announcer:
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