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How Do I Optimize Treatment in Patients With Myelofibrosis and Moderate to Severe Thrombocytopenia?

Announcer:
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Dr. Mascarenhas:
Hi, I'm John Mascarenhas from the Icahn School of Medicine at Mount Sinai, New York, and today I'm going to be talking about the management considerations of patients with myelofibrosis and thrombocytopenia. Here you'll see that there is a clinical phenotypic spectrum of myelofibrosis that ranges from proliferative to cytopenic myelofibrosis. And although these are not always uniform in presentation, the cytopenic myelofibrosis patient is typically that patient who has primary myelofibrosis, often presents with cytopenias, anemia and thrombocytopenia, or both, and may have less prominent splenomegaly and leukocytosis.

The driver mutations can be present in any side of the spectrum. But often in the cytopenic MF patient, it is a low JAK2 allele burden or JAK2 wild type for triple-negative patients that you find here. These patients unfortunately do worse than the patients on the proliferative side with a worse overall survival and a higher incidence and rate of leukemic transformation.

So this is the clinical phenotype and the spectrums that one can see with myelofibrosis, and it's important to understand that thrombocytopenia as that hallmark feature of the cytopenic myelofibrosis patient is a common clinical variable that's seen. And at least 25% of patients at the time of diagnosis will have a platelet count of less than 100,000. Somewhere between 10 to 15% may have a platelet count less than 50,000, and this worsens and increases over time. So as the disease progresses and worsens, the degree of thrombocytopenia and the frequency of thrombocytopenia also increases. And this is a hallmark of progressive disease.
Here you'll appreciate that thrombocytopenia also likely associates with other clinical variables of significance. So if you segregate patients by platelet counts less than 100,000 in darker color or greater than 100,000 in the lighter shade, you can see that patients with thrombocytopenia tend to have higher symptom severity across multiple symptom burden types, particularly as it relates to fatigue, early satiety, which is typically a spleen related complaint that one thinks of, inactivity, dizziness, sad mood, night sweats, itching, weight loss, and overall quality of life. So severe thrombocytopenia is also a biomarker for severe disease and severe symptom burden.

What I'm showing you here is an analysis that was done off of the PERSIST studies looking at thrombocytopenia versus anemia and its relationship with symptom score, physical functioning score, and spleen-related symptom scores. So in each case in this analysis, whether it's from PERSIST-1, no matter which TSS form was used, or PAC203, which is the phase two dose finding study, low platelets was actually associated to a greater degree with increased symptom burden than low hemoglobin, worse median physical functioning scores and greater spleen related symptom scores as well. So sort of not what one would typically think of, and the association of thrombocytopenia with significant symptom burden and individual symptom entities.

Now, it's also important to realize that thrombocytopenia itself is not just a common clinical feature and worsens with time, but also is an early indicator of poor prognosis. So patients with significant thrombocytopenia, and this is reflected in the DIPSS+, for example, the

scoring system that helps risk stratify patients. Thrombocytopenia is independently associated with poor outcome. And what I'm showing you here is a study looking at the depth of thrombocytopenia and survival in patients with myelofibrosis. So platelet count greater than 100,000, a median survival of 57 months, platelets of 50 to 100,000, median survival of 44 months, and a platelet count less than 50,000, a median survival of 15 months.
So significant difference in survival with low platelets where you have a higher risk of leukemia transformation often associated with higher degree bone marrow fibrosis and tracks with anemia and leukopenia. Of course, anemia is also an independent clinical variable for poor outcome.

And here I'm just showing you to impress upon you the fact that thrombocytopenia is recognized when doing multi-variable analysis to be an independent risk factor for survival. This is from the DIPSS series, the Dynamic International Prognostic Scoring System, in which the five clinical variables for the DIPPS were also integrated with low platelets, less than 100,000, red cell transfusion dependence and unfavorable carrier types. So cytopenia is having a direct impact and contribution to scoring systems as first witness by the DIPSS+.

Now, if one were to look at other risk factors that associate with thrombocytopenia to give you sort of that fuller picture, this is from a Spanish registry, you can see that platelet counts less than 50,000 were more likely to be seen in patients with myelofibrosis that were older in age, were more likely to have bleeding manifestations as one would expect, a lower hemoglobin because thrombocytopenia and anemia do tract together, higher degree of circulating blast, a higher degree of bone marrow fibrosis, and were enriched in the higher risk scoring systems, whether it's IPS or DIPSS. Again, playing into the idea that this is an independent prognostic factor that can associate with multiple variables that are known to predict a poorer survival.

And what do you do in someone who has myelofibrosis and low platelets? Well, the options are unfortunately limited as shown here. This is from the same series from the Spanish registry. You have a lot less cytoreductive agents like hydroxyurea and JAK inhibitors that can be used in these patients with extreme thrombocytopenia, more red cell transfusional support in ESA use, more Danazol and immunomodulatory drugs to try to improve concurrent anemia, and even drugs like corticosteroids which are infrequently used in the US to treat aspects of myelofibrosis. Really the take-home message here is that we don't have great drugs historically to treat our patients with myelofibrosis.

Of course, ruxolitinib was the first approved JAK inhibitor for myelofibrosis and is an excellent drug to address spleen and symptom burden, but is a myelosuppressive drug as a JAK12 inhibitor. And here I'm showing you the predictable cadence of treatment emergent thrombocytopenia in which you get about a 40% median reduction in platelet count off the bat with ruxolitnib, and then stays rather stable through the treatment course. And then of course, the change in anemia hemoglobin is predictable in nadir within about two to three months and then sits around one gram per deciliter from where you started. So this is not a drug that can be given in patients or at least at adequate doses in patients with low platelets and has an expected treatment emergent thrombocytopenia profile.

So what do you do with patients who have low platelets that are in need of spleen or symptom reduction? And this is an adaption of the NCCN guidelines where it bifurcates. If you have platelets less than 50,000, the options include clinical trial or commercial available pacritinib, which is the only JAK inhibitor that's labeled for this low platelet, less than 50,000 population and or transplant. And I don't think these are mutually exclusive. Some patients can receive pacritinib and route to transplant and it's likely a ideal way of treating some patients that are transplant eligible.

And of course if platelets are greater than 50,000, you have ruxolitnib or fedratinib. If they do not succeed or lose response, you can use alternative JAK inhibitors including pacritinib here as endorsed by the NCCN guidelines irrespective of platelet count. If one looks at the data that led to the approval of pacritinib, as we've been talking about, this is from the PERSIST-2 study. Pacritinib at a dose of 200 milligrams twice daily, which is the approved dose, was far more significantly associated with spleen volume reduction than best available therapy, which also included in half the patient's ruxolitinib. So 22% versus 3%, and symptom improvement was significantly better with pacritinib at 35% versus 14%. And this was particularly true if you looked at the patients with platelet counts less than 50,000, which is where the label ended up 29% versus 3%, and 26% versus 9%. So spleen and symptom benefit, even in extreme thrombocytopenia with pacritinib.

A recent retrospective analysis would also... Comparing pacritinib to those ruxolitnib treated patients in the BAT arm, would also make the point that pacritinib is superior to low dose ruxolitinib five milligrams twice daily when looking at spleen volume reduction, symptom score improvement, and patient global impression of change. It is also in most cases superior to low-dose ruxolitinib when looking at individual symptom scores themselves.

And here this is data from PAC203, simply providing some sense of the kinetics of platelet count when dosing with pacritinib and the triangle, the blue triangle, are those that received 200 milligrams twice daily, the approved dose, and there's about a 25% median change in platelet count within the first four weeks. But quickly by week 12, it's back to baseline. And after week 12, there's a sense of potential increase in some patients. And I can say anecdotally, you do get in some cases significant increase in platelet count and

anemia after 24 and 36 weeks of treatment with pacritinib.

So, in summary, thrombocytopenia is a poor prognostic marker. It associates with this cytopenic myelofibrosis patient population. It is recognized in the risk scoring systems as an independent influence on survival and leukemic transformation. There are unfortunately very little agents that can be used successfully in this area of patients with spleen and symptom burden effectively, and pacritinib remains the only approved drug for patients with extreme thrombocytopenia or endorsed by the NCCN guidelines for patients after failure with an initial JAK inhibitor. So with that, I'll end, and appreciate your attention.

Announcer:
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