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How Do You Define and Manage No Response or Loss of Response to JAK Inhibitor Therapy?

Announcer:
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Dr. Verstovek:
Hello, I am Srdan Verstovek, professor of medicine in the leukemia department at MD Anderson Cancer Center in Houston, Texas. Today I'm going talk on how do you define and manage no response or loss of response to JAK inhibitor therapy. According to NCCN guidelines on a therapy for myelofibrosis and specifically focusing on people with advanced features, so-called high-risk myelofibrosis patients, we would see that we initiate therapy where the symptom burden is significant, and then look at the platelet number as a determining factor which JAK2 inhibitor to consider to control the symptoms.

I'm talking about the symptomatic improvement in the spleen and general systemic symptoms, night sweating, low grade fevers, itching, bone aches and pains and others. Pacritinib is approved therapy since February of 2022 for patients with platelets below 50. So that's the number one choice. As we know ruxolitinib and fedratinib are choices for patients with platelets above 50, one or the other can be used.

Now when we face a no response or loss of response situation, then the guidelines and the current practice indicate that any alternative JAK inhibitor can be used as alternative. For example, after ruxolitinib, one would consider fedratinib or even pacritinib, regardless of the platelet number. If we start with fedratinib, ruxolitinib or pacritinib can be used. So combinations exists, but the key parameters here is a no response or loss of response definition.

A definition does not really exist of a loss of response or no response. There is no consensus definition as listed on this slide. We talk about the primary resistance or refractiveness typically, but I should say almost everybody has, any patient, a degree of improvement with any JAK inhibitors. So primary resistance is very rare. Relapse or loss of initial response is much more common and we call this many times a secondary resistance, a splenic relapse or loss of control of the symptoms.

But there is also intolerance or a progression of the disease, which is anemia or thrombocytopenia. In fact, most of the time, anemia or cytopenia in general is the leading cause for stopping ruxolitinib. Disease progression with the disease progressing to acute mild leukemia is another possibility unrelated really to a JAK inhibitor use. The definition of ruxolitinib treatment failure in clinical trials also varies from one study to another.

So we really face, even when we talk about the clinical study execution, we lack the definitions. Now in everyday practice, the durability of ruxolitinib as a first line choice may vary. In the clinical studies, we know that the average duration is about three years, and then something else needs to be done. Unlike any other study, what you can see here in the red color is the experience in people with low platelets. This is in a black color, and you can see here that the average duration is very short. After ruxolitinib outcome is poor.

And again, there are factors that would determine who does better than the others. For example, platelet numbers or blasts or genetic

complexity. These are all the factors that can determine the outcome and certainly there is an unmet need here in terms of providing benefit to people who are by and large cytopenic. When we look at the fedratinib use in a secondary setting, we look at the analysis of a Phase II open label study called JAKARTA2.

Now this is in patients that were previously treated with ruxolitinib, and we have about a 27% to 30% response rate as you can see, which is very valuable. But at the same time, we have to acknowledge that fedratinib worsens anemia and thrombocytopenia and has some gastrointestinal side effects and black box warnings for encephalopathy, which is a result of a thiamine deficiency. And encephalopathy is a very rare side effect of thiamine deficiency, but one needs to measure thiamine and supplement it if necessary.

So, in this setting, recent approval of pacritinib is very welcome. The PAC 203 study was a study in people who were previously treated and were refractory, resistant, and intolerant to ruxolitinib and have platelets below 100, which is quite common in a secondary setting. As you can see, 31% of evaluable patients, even with platelets below 50,000 had a response in the spleen and a very good number of patients, about 27% of them even had improvement in the TSS, total symptom score in a range of a 50%.

At the same time, in that PAC203 study in the second setting with patients having platelets below 100, we see on the left side that the platelets were normal or stable to be correct, over time during the therapy, while some patients, as you see to the right had improvement in anemia. So an anemia response is a possibility when you use pacritinib in the secondary setting.

And here we come to the MOMENTUM study. The MOMENTUM study is a Phase III, random study of momelotinib versus danazol, a MOMENTUM study is under review for possible approval of momelotinib therapy for patients with anemia and symptoms because as you see on this slide, this was a study designed for patients that were symptomatic with anemia and platelets above 25,000 with the key parameters in assessment of the quality of life improvement and anemia benefits.

And in this setting, this transfusion independence rate achieved at week 24 is quite significant. Many patients in the second setting are very anemic, and you see to the left, a 31% of the patients on momelotinib were transfusion independent after 24 weeks of therapy. To the right, you can see how hemoglobin levels improved, and were stable over time at the higher levels than at the beginning. And of course, MOMENTUM also outlines the benefit of momelotinib on the spleen and symptoms.

Because this is a JAK inhibitor, you do have improvements in these two parameters as well. In summary, cytopenia and myelofibrosis is a marker of poor prognosis disease, which we know very well, but also affects choices and abilities of therapies we choose to provide optimal benefit and provided for long period of time. Standard therapy options are limited and new therapeutic options that have recently been approved like pacritinib are in development for possible approval in the near future like momelotinib are very welcome. Thank you very much.

Announcer:
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