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Assessing Response to Targeted Therapy in Non-Advanced Systemic Mastocytosis: How to Distinguish AEs From Disease Symptoms

Announcer:
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Dr. Radia:
Hello, my name is Deepti Radia. I'm a Hematology Consultant at Guy's and St. Thomas' Hospital in London. I'm going to be talking to you about how to assess response to a targeted therapy in patients with non-advanced systemic mastocytosis or indolent systemic mastocytosis: how do you distinguish adverse events or side effects from disease symptoms?

So looking at which patients really are considered for targeted therapy, if they have a diagnosis of non-advanced or indolent systemic mastocytosis, these are patients who are on polypharmacy with multi anti-mediator treatments, more than two or three regular medications which have been optimized. And regardless of that, they still have inadequate symptom control. They have multiple organs affected and it affects their ability to function on a daily basis. And really, these patients may have multiorgan symptoms as shown by the cartoon in the middle. And the tyrosine kinase inhibitor to consider is avapritinib 25 mg once daily. But how well is it tolerated? And what effects – what side effects do patients actually report?

So this would be reflected in the PIONEER study, which is the first randomized double-blind placebo-controlled study in patients with symptomatic ISM, or indolent systemic mastocytosis. And you can see from the trial design, that patients had to be on best supportive therapy optimize for at least 2 or 3 months and a month, at least a combination of two or more. And the Part 1 of the trial, which was the dose-finding phase 1, randomized patients between doses of 25 mg once daily, 50 mg once daily, 100 mg once a day, and placebo. And you had 10 patients in each arm, or the placebo of 9. And that determined the Part 2 dose. And the Part – recommended Part 2 dose was 25 mg once daily. And patients were double-blinded in the first period of the treatment. And it was a 2:1 randomization of either getting the avapritinib at 25 mg, 141 patients got that, or placebo, which 71 patients received. And then there was a crossover and open-label extension study.

So baseline characteristics of patients, as you can see with the placebo, and on the actual trial arm, there was very little difference between their age. And the majority of patients were significant number of female, more than 70%. Really focusing on the symptom burden score, you can see the total symptom score was fairly high on those patients with 50.2 and 52.4 across the board, similar, with the most severe symptom score, scoring 7.7. And these scores range from 0 to 1. We're looking at the fact that they all had a diagnosis that was centrally confirmed of indolent SM, and looking at the fact that some had actually had previous cytoreductive therapy prior to being enrolled in the trial to try and manage their symptoms. And you can see that there were a combination of multiple polypharmacy in order to help manage their treatments, including anti-IgE antibodies and corticosteroids.

So this is actually – this waterfall plot is actually quite significant. The end point of the trial was looking at significant symptom improvement by more than 30%. And what this shows us that the mean total symptom score changed from baseline at 48 weeks was

significant across all the symptom domains. So the most symptom – most severe symptoms score per patient, and then the symptoms for the skin which were flushing, itching, and the degree of the spots or the lesions; abdominal pain, which was significant diarrhea, severity, nausea; neurocognitive symptoms of brain fog, headaches, and dizziness; bone pain, and generalized fatigue, you can see that those patients who were on avapritinib had a much better improvement of their symptoms from baseline compared to placebo.

But what about the patient's safety? So the majority of patients, so we're looking at the 141 patients on the drug compared to the 71 patients on placebo. Majority of the adverse events reported were grade 1 or 2 with the low rate of discontinuation across the trial. There were more SAEs reported in the placebo arm reflecting that the disease can cause symptoms like headaches, nausea, and some peripheral periorbital edema. But really, one of the side effects to watch out for are is periorbital edema, which is a known side effect of TKIs and peripheral edema. The nausea and the headaches and the dizziness, really, you can see that more headache was reported in the placebo arm as well as the dizziness being equal in both. So the most common side effects that actually of the TKI that we need to be aware of are the periorbital edema. And so when I'm treating patients with a TKI, they're generally well tolerated. They can overlap the symptoms with those of the mediator symptoms which we've seen on the placebo arm. And the most important thing is really to have a baseline of the clinical history of that patient, and how their symptoms, SM symptoms, affect them to know what difference a TKI makes, and note the triggers for those patients. And then again, using a Symptom Assessment Form that's objective with the qualitative information that you've got description for the patient, you can see how the TKI has made a difference in that patient's disease and are able to think about what are the side effects. Like I've mentioned before, periorbital edema is a known side effect of TKIs.

It is less severe on the lower doses of 50 mg versus the 100 or sorry - 25 mg, versus 50 or 100-mg doses. And really, the management is when you consent the patients to the drug, let them know that they're going to get a little bit of swelling under the eyes. It will be worse in the morning and will get better in the evening due to gravity. If it's very severe, a low dose of diuretic may be used. Peripheral edema, again, known side effects and depends on whether any other comorbidities and whether or not patients might need diuretics. It's dependent edema, so ask patients to elevate their legs and it will get better. And if it's significant, you might need a low dose of diuretics. With nausea you can take antiemetics. And please remember that TKIs should be taken on an empty stomach 2 hours prior to taking the dose of the tablet and not eat for at least 1 hour post to reduce that nausea that can be reported. And again, when I consent patients, I tell them their hair is going to go white. That is the effect of the TKI on melanocyte, and patients definitely get whitening with their hair color regardless of what their baseline hair color is.

Thank you.

Announcer:
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