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When Best Supportive Care Is Not Enough: Who Is Eligible for Targeted Therapy in Non-Advanced Systemic Mastocytosis?

Announcer:
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Dr. Radia:
Hello, my name is Deepti Radia. I'm Hematology Consultant at Guy's and St. Thomas' Hospital in London. This section I'm going to be talking to you about when is the best supportive care not enough who is eligible for targeted therapy in indolent or non-advanced systemic mastocytosis?

So you all know currently the therapeutic options for symptom management in patients with indolent systemic mastocytosis, ISM patients, is really a combination of anti-mediator therapies. Patients get symptoms because of the mediator release from their mast cells when they are triggered. And the combination of anti H1 antihistamines, anti H2 antihistamines, mast cell stabilizers, antileukotrienes, you tricyclic antidepressants, and essentially gabapentin analogs or steroids can be used in various combinations and various doses in order to try and manage the symptoms of some of these patients.

For those patients who have anaphylaxis secondary to venom toxin, such as a Hymenoptera allergy, and they have an identified antigen, then ITT, or immune tolerance therapy, is really the mainstay of treatment. So we tell the patients to avoid triggers, we give all patients with ISM adrenaline auto injections regardless of whether they've had anaphylaxis, and we judge and titrate the doses of the medications in order to try and keep their symptoms under control. And there may be a number of patients who had, regardless of the polypharmacy, they really do not manage their symptoms, and their quality of life can be impacted on. And these are patients where we've been considering having cytoreductive therapy in the past, or now in the context of trials, tyrosine kinase inhibitors.

So a patient, again, as just reiterating more than three or four regular medications of anti-mediator therapy, multiple organs affect inability to function, high symptom burden, inadequate symptom control, those should be the patients you should be thinking about in order to consider them for a tyrosine kinase inhibitor.

So the focus on the current and only trial – registrational trial for PIONEER study is about avapritinib. Avapritinib is a tyrosine kinase inhibitor, and PIONEER is a study that randomized double-blind placebo-controlled study, patients with symptomatic indolent systemic mastocytosis, who had been on best supportive therapy for which had been optimized for 2 to 3 months. You can see the eligibility criteria here. And what happened with the Part 1 is that patients were randomized between doses of 25 mg once daily, 50, 100, and a placebo. And then for the Part 2, the recommended Part 2 dose was 25 mg once a day, it was a 2:1 randomization to the drug, avapritinib, or placebo. And the data from the PIONEER study, which was the first of its type, show – with the end point looking at improvement of quality of life based on a symptom – Objective Symptom Assessment Form, as well as looking at safety, and disease burden.

So the Symptom Assessment Form that was used was the ISM-SAF, which was constructed specifically, as a PRO tool, and has been

used in several trials. And it really looks at 11 domains, which affected most patients, and it scores them from a 0 where they don't have any symptoms to 10 is a worst ever symptom. And it analyzes a diary on a 2-week rotating basis, because we know that patients have good days and bad days. So the average over the 2 weeks gives you a better objective idea. And the score, the total symptom score is from 0 to 110.

And when you looked at the data from the trial, you can see that those patients who were on the drug actually had more improvement. So that's looking at the patients with the blue, had a better improvement in their symptom control than those on placebo. When all the patients went on to the rollover part, which meant all the patients were on avapritinib at 25 milligrams, those with the placebo on the red line or the burgundy line on the graph, caught up with those patients who were on the drug. So there was an improvement from baseline of the Symptom Assessments Forms and the symptom reported outcomes from patients when they were on the drug and on the Part 2 rollover.

So I'd like to highlight how symptomatic patients can be with a disease that's labeled as indolent systemic mastocytosis. So this particular patient case that I want to share was a patient who consented to take part in the PIONEER trial in March 2021, and had a screening visit in May 2021. And his symptoms are highlighted in the first box. Fatigue, severe pruritus, intractable pruritus, some gastric symptoms, cognitive issues, and the current medications or polypharmacy we were talking about are highlighted in the middle. His blood tests showed that he had normal full blood counts and normal biochemical screen, which is what you'd expect for indolent disease, and his tryptase level was 102 at the time of enrollment, His bone marrow trephine confirmed the diagnosis of indolent systemic mastocytosis. So he started on the PIONEER trial, and on Part 2, which meant he started either on the placebo or the 25 mg once a day of avapritinib. And the review in March, the baseline was, as I've mentioned earlier, but a month later, he tells us the skin improved – is looking better. He was less itchy. Seeing him, his skin rash was visibly lighter in color. He was sleeping better. He said his gut motions are still loose, his weight was stable, and his appetite was stable. And what we noticed as a side effect or an adverse event was that he had grade 1 periorbital edema. He had swelling around his eyes, but he had no changes in the medications that we'd previously discussed. Three months later, although it was double blind, knowing that his skin had much improved, he had much less itching, visibly examining him the macules are flatter, he wasn't as red, he was lighter in color, he was sleeping much better, he was less tired, and his gut symptoms were stable. And the grade 1 periorbital edema was still present as part of being on the drug. And he stopped his cetirizine and he reduced his antihistamine, so you'd reduce his fexofenadine. So on the back of the trial, he was getting some benefit, and he reduced his anti-mediator therapy as we went along.

And 9 months later, his skin is much better. And this is him sharing photos. This was his skin at baseline, and this is all across his body. The only part that was spared was his face. And at 9 months these are much flatter, and you can hardly see the redness and there are not as much – are not as raised, and he did not have the itching. Fatigue, as we've said, sleeping was much better. And his tryptase had come down from 102 to 75. But the reason for putting in the boot photograph really is that you have no idea about the quality of these patients' life. As a clinician, I can see how severe the symptoms were, how they're impacting on him, I was having a discussion with him. But actually, he came in at that point 9 months later with these pair of boots on and he marched into the clinic appointment, and he said, 'Dr. Radia, look at my feet. Look at my feet,' and I saw the boots. And I remember him telling me that at the very beginning, he had never been able to wear closed shoes for at least 6 years. He hadn't been able to put a pair of socks on. He wore open sandals with tiny straps. And even in the winter, he went out shopping with those. So I think that picture means a lot about what difference that TKI made in this particular patient's quality of life. And I think when I remember him, I remember the boots more than the actual skin photos that he shares.

So in summary, patients with indolent SM can have debilitating disease symptom burden despite being on polypharmacy multi anti-mediator medications. Those patients who need two or more anti-mediator treatments and are suboptimally controlled regardless of optimizing the doses should really be considered for TKI treatment. The avapritinib at 25 mg once daily in PIONEER demonstrated significant improvements in the symptom burden for symptomatic ISM patients. And avapritinib at 25 mg showed significant improvements in reducing the mast cell burden which was visible in the cutaneous lesions but also proven on biopsy, reduction in tryptase levels, and in skin or bone biopsies.

Thank you.

Announcer:
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