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How Should I Evaluate Treatment Responses in Non-Advanced Systemic Mastocytosis?

Announcer:
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Dr. Giannetti:
Hello everybody. Thank you for your attendance. My name is Dr. Matthew Giannetti. I am an allergy immunology faculty at the Brigham and Women's Hospital in Boston, Massachusetts. I'm also an assistant professor of Medicine at Harvard Medical School and the associate director of the Brigham and Women's Mastocytosis Center. So I'm here talking to you today about a variety of different topics in systemic mastocytosis. The particular topic of this talk would be how to evaluate a treatment response. This is for mastocytosis in general, but more particularly, for the targeted tyrosine kinase inhibitor therapies.

I wanted to start a little bit with a case, kind of, study here because it provides some context for how to think and how to approach these patients, but also how to gauge what has improved, how is it improved, and then do we need more medication, et cetera. So this is one of my patients. We're going to call her here KA. She's a 59-year-old lady with quite a long history of mastocytosis. So, really, her disease started quite benign when she was in her 20s, 30s as cutaneous lesions. So she first developed spots, generally truncal spots, up her thighs. And then over the course of the next 20, 30 years, she began to accumulate symptoms. This included gastrointestinal symptoms, this included additional cutaneous symptoms, and finally, constitutional symptoms. This occurred in context with a rising serum tryptase. And so her most updated, kind of clinical characteristics, symptoms, and medications here are as follows. Tryptase.

A good elevation in tryptase. Her baseline is around 135 nanograms per milliliter. In her bone marrow, this is not the comprehensive bone marrow biopsy, but I've picked and chose a bit here. About 20% of the cellularity is a mast cell burden and she has a high fraction of KIT D816V allele fraction as well. I didn't include in here, but there's no evidence of other myeloproliferative disease. She does not have any other driving mutations that are associated with other myeloproliferative disorders. So really pure systemic mastocytosis driven by the KIT D816V mutation. A fantastic patient for targeted therapy based on this molecular profile I would add. Symptoms that she has, lots of gastrointestinal symptoms. Bloating, diarrhea, cramping. These occur both at baseline, but with episodic peaks, if you will. Skin, she has itching, redness, and flaring of her spots particularly in response to temperature, which is quite common.

And then finally, more constitutional symptoms, such as fatigue. And I would also add some neurologic or psychiatric symptoms. So a little bit of what is termed brain fog, kind of mental slowing, difficulty concentrating. You know, symptoms that are disruptive to her day-to-day functioning as a high-functioning professional. Medications, a reasonably trim list. So cetirizine. She's taking 10 milligrams twice a day. Famotidine, 20 milligrams twice a day. And oral cromolyn, 200 milligrams four times daily. And despite all of these medications, she is still really not doing well. So as of this time, we had a discussion about entering a clinical trial for a targeted tyrosine kinase inhibitor. Keeping that patient in mind, I want to walk you through some of our newer literature here about how we're gonna assess treatment response.

So, as you guys are of course listening as the audience is listening to this talk, I wanna try to bring on some up-to-date kind of theories

and monitoring of symptoms. So as we started having more clinical trials available, a lot of the leading experts in the mast cell field got together and thought about how are we going to best assess some of these patients? For those with the more advanced variants, it's a little bit easier, frankly, because they have very clear abnormalities, such as portal hypertension, ascites, et cetera. For indolent, in the non-advanced variants of mastocytosis, it's a bit more challenging because most of the disruption in quality of life is not necessarily impacting quantity or life expectancy, but it's more the morbidity or the decrease in quality of life. So as you can see here, the favorite approach which was published really just a couple of months ago in the Journal of Allergy Clinical Immunology: In Practice is a tiered approach across multiple different domains.

So, I'll kind of walk you through this here. Tier one is symptoms. So this is basically what are the symptoms patients are experienced? We use patient-reported outcomes or PRO. This is the abbreviation you might hear on how to measure some of these. We have a variety of different patient-reported outcome scores, Mastocytosis Activity Scores, ISMSAF, which is a proprietary one, but a bunch of different scoring systems that gets at what are the skin symptoms, what are the GI symptoms, what are the constitutional symptoms, et cetera.

The second is the overall quality of life. You know, this is generally intimately related with some of the symptoms, but it's a little bit different. More of the focus is because of these symptoms, are you able to work? If so, are you limited in your work? Do you feel you're able to perform your best work, et cetera? Then we move to more objective signs. So does the patient have osteoporosis? Do they have cutaneous lesions? About 85% of patients with indolent systemic mastocytosis will have cutaneous mastocytosis as well. Laboratory values. So what is their baseline serum tryptase? Do they have the KIT D816V mutation? If so, what is the allele frequency of that mutation? And then for some of the more advanced variants or smoldering systemic mastocytosis, is their liver or their spleen or their lymph nodes enlarged?

And if so, how much? So all of these try to get at different domains of a single patient with a non-advanced variant of mastocytosis. Okay, so say we have scored all of these domains, how do we actually assess whether the patient is better or not? So this part is a little bit easier. We've basically divided it into four different categories based on the degree of response. So you see here complete response defined by an improvement of greater than 90% in any one individual domain. So, for example, if tryptase was a hundred and it goes down to five, that's a 95% reduction in the serum tryptase. That would be defined as a complete response.

Major response is defined by improvement greater than 60%, but less than 90%. So between 60 and 90%. Partial response defined by improvement between 30 and 60%. And then finally, no response is less than 30%. So, you know, the response scoring gets a little bit complicated when you're talking about multiple domains and then within each domain whether they're complete, major, partial, et cetera. But I think, really, it's a fantastic way to get at the different aspects of the quality of life, labs, et cetera involved in treating these patients with mastocytosis. So this here is just an example of how tyrosine kinase inhibitor therapy can improve cutaneous lesions. As we mentioned, one domain was termed signs. Signs can be osteoporosis or it could be cutaneous lesions. This here represents a phenomenal improvement.

We do have fancy computer-generated objective ways of scoring symptoms, but you can simply look at this. This is almost a complete resolution. I would say this is a complete response here in terms of cutaneous symptom scores. Moving on at some of the symptom scores, this here is the Mastocytosis Activity Score. Again, there's a couple of other symptom scores, but this one is publicly available and published and available for any investigator to use or simply clinicians treating patients with mast cell disorders. I like the Mastocytosis Activity Score because it really hits all important domains of symptoms within systemic mastocytosis. And then it allows you both to do how severe were the symptoms, but also kind of going on a day-to-day basis, so you can kind of track it. So you would see here for any individual patient, day one, two, three, four, five, six, seven, et cetera. And each can be scored not at all, mild, moderate, severe, or very severe. And the days are really important rather than in individual measurement because my anecdotal experience with this disease is that it can vary quite a bit actually. So one day patients may not have much symptoms of itching, but that does not mean that their disease has gone away. It does very much fluctuate.

Okay, so going back to this patient here, pre-tyrosine kinase inhibitor, we talked about these and one year post-tyrosine kinase inhibitor. So we're not going to do the whole all five tiers, but we're going to do just this information here and I just want people to get the flavor or the feel of how to look at this. So looking at tryptase, 135 to 25 is approximately an 81% decrease. Looking at the KIT D816V allele fraction, 82% decrease. This is a very high allele fraction and a considerable decrease actually. Because both of these decreases fall greater than 60% but less than 90%, in fact, I would say that that's a major response based on this here. Skin lesions, about 70% scored on symptom scores. So again, that classifies as a major response. So using this particular symptom scoring and monitoring, I would say this is a major response to targeted tyrosine kinase inhibitor therapy. So in general, a couple of the points of the summary and evaluation of treatment response. As with side effects, time to response differs considerably based on the dose.

The dose is much higher in the advanced variants of the disease. And concordantly, the time to response is much quicker. So I would

say for most patients, three to six months at minimum to observe symptoms for a lower dose tyrosine kinase inhibitor. And in many patients, it's even longer than that. These patients need to be assessed on an ongoing basis, ideally monthly or at minimum every several months to monitor symptom improvement, side effects, tolerability, et cetera. Repeat bone marrow biopsy may be necessary. Generally, it is necessary depending on how symptoms are going. For sure necessary if there's any significant clinical changes. And then finally, if tryptase does not trend to less than 11.5 nanograms per milliliter, I would consider testing for hereditary alpha tryptasemia. So again, thank you very much for your time and for listening. Very nice to be talking with you today. Again, my name is Dr. Matthew Giannetti. Thank you.

Announcer:
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