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How KIT D816V Shapes Systemic Mastocytosis Diagnosis and Treatment

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is sponsored by Blueprint Medicines, a Sanofi company. Here's your host, Dr. Brian McDonough.

Dr. McDonough:
This is *Clinician's Roundtable* on ReachMD, and I'm Dr. Brian McDonough. Here with me today to evaluate how the KIT D816V mutation can inform treatment decisions in systemic mastocytosis is Dr. Thanai Pongdee. He's the Research Chair in the Division of Allergic Diseases and an Associate Professor of Medicine in the College of Medicine and Science at the Mayo Clinic in Rochester, Minnesota. Dr. Pongdee, welcome to the program.

Dr. Pongdee:
It's a pleasure to be here. I appreciate the opportunity to speak with you today.

Dr. McDonough:
So let's start with some background, Dr. Pongdee. Can you walk us through the role of KIT D816V in driving mast cell proliferation and activation and explain why it's such a defining feature of systemic mastocytosis?

Dr. Pongdee:
Yeah, I think that's a great question to open up the conversation. So mast cells can be turned on per se or activated where they do lots of different things. They have a receptor on the surface called a KIT receptor, and you can think of this as a keyhole where it has to be turned in the on position for it to do all of its activities. And normally, you need something called stem cell factor in the immune system, which is like the key that goes in this keyhole to turn the mast cell on. But in mastocytosis, there's a mutation in this KIT receptor in the keyhole. So this keyhole is always turned on. You don't need a key anymore to activate it. It just turns on by itself.

So this mutation is found in greater than 90 percent of patients with mastocytosis. So it really is the key reason that's driving the disease because, again, this activation key is always turned on regardless. And so the mast cells are always activated, causing lots of symptoms. And since it's found in so many people, it's something that we always look for.

Dr. McDonough:
With that background in mind, let's bring this into the clinical practice setting. How do molecular findings like KIT D816V help you differentiate between indolent and advanced systemic mastocytosis?

Dr. Pongdee:
Yeah, regarding indolent disease, for the vast majority of patients that have systemic mastocytosis, that's the form that they have. And again, this KIT D816V mutation is found in greater than 90 percent of those patients. It is the defining mutation. It's something that we always look for. We can test for it in the peripheral blood with fairly high accuracy, so we don't always have to have an invasive procedure like a bone marrow biopsy. So again, it's very helpful in diagnosis. It's very helpful to know about in terms of thinking about how we're going to treat the disease.

In the advanced form of systemic mastocytosis, there's often other gene mutations that we find that drive that disease, and that's why with multiple mutations, we know there's higher risk of other issues, such as organ damage and increased risk of lots of long-term issues in the advanced form of the disease that we don't always see in the indolent form.

Dr. McDonough:

Now, historically, management has focused on symptom control. But what impact has the recognition of KIT D816V had on your overall treatment approach?

Dr. Pongdee:
Yeah, it has really transformed how we think about treatment regimens for patients. For decades, all we really had were medications to treat the symptoms, so it was what we call a non-targeted approach. So depending on the symptom that a patient had—whether it be skin symptoms or gastrointestinal symptoms—we had an array of medicines to treat those symptoms, but at the end of the day, those mast cells were still always activated.

Now that we have what we call targeted therapies that really target that KIT receptor and mutation, we can in essence turn that off. So when that KIT receptor was always turned on because of the mutation, we now have medicines that can actually turn that off. And when you turn that off, mast cells actually will go away. So we see decreased mast cell numbers in patients that receive those kind of medications, and then if you have decreased numbers, consequently, you have decreased symptoms. So it's a more advanced way we can target the root cause of the problem rather than just treating all the symptoms that come from it.

Dr. McDonough:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Dr. Thanai Pongdee about the clinical implications of KIT D816V in systemic mastocytosis care.

So, Dr. Pongdee, let's continue our conversation by taking a closer look at how these molecular insights are influencing treatment decisions and patient management. In practice, how are you using KIT mutation status to guide treatment selection, particularly when you're deciding whether to continue supportive care or introduce a targeted approach?

Dr. Pongdee:
In terms of therapy, it's very important to know because now if we know a patient has that mutation, we have medications available to target that mutation. I will say in the clinical trials, the targeted therapies, even though we focused on that D816V mutation, there are a percentage of people in clinical trials that did not have that mutation detected but still responded to these therapies. And it's important to keep in mind that the absence of that mutation does not mean you're not eligible for some of these newer targeted therapies because in the trials, that very specific mutation was the only one looked for, but we know there's other similar mutations in that KIT receptor that we just didn't look for but still seem to respond to the targeted therapy.

In terms of treatment selection, that very much depends on that individual patient's symptoms and what that patient's goals are. So if someone's not doing well on multiple symptom-directed therapies, that's probably an easier scenario: "Oh, well, we obviously need to do something different." But some patients may be okay, but they have to take four or five different medicines a day. And the potential that targeted therapy could reduce that polypharmacy burden over a long time is very appealing to many patients. So that's another consideration to think about—not only are patients refractory to current therapy, but are they wanting to change the therapy that they're currently on?

Dr. McDonough:
Now, if we examine the current guidelines, they emphasize that routine KIT mutation testing should be part of our standard diagnostic workup. And when it comes to treatment, they recommend targeted therapy for advanced systemic mastocytosis, while a more individualized approach is appropriate for indolent disease. With that in mind, can you tell us how you interpret these guidelines in your own practice?

Dr. Pongdee:
Yeah, I think the guidelines detail this quite well. In the diagnostic process, because the presence of this KIT D816V mutation occurs in so many patients with systemic mastocytosis, that really is a key feature to make the diagnosis. So if one's not sure—because again, it can be hard to make the diagnosis because many of the symptoms are multi-organ in nature; there could be lots of other potential reasons to explain the symptoms—and mastocytosis is being considered, if you're able to detect a presence of that mutation, that would really steer you to making the diagnosis of that disease.

In terms of the therapy, advanced systemic mastocytosis has a much higher rate of morbidity and actually mortality perhaps depending on the form. And so targeted therapy where you're actually eliminating mast cells from an individual is a higher priority because in that particular patient with advanced disease, you have mast cells invading different organs and causing organ damage, and consequently, you have significant organ pathology, which could certainly impact one's long-term health in a very negative way.

In indolent disease, many of those patients have more chronic symptoms, so we don't typically see issues with mortality or progression of disease in the indolent systemic mastocytosis population. So their targeted therapy is considered a little more optional depending,

again, on the patient preferences and their individual symptom presentation. Because targeted therapy—although effective—has potential side effects that need to be considered, so in a chronic disease state, it's important to balance the pros and cons of choosing targeted therapy.

Dr. McDonough:
In our final few moments here, Dr. Pongdee, let's bring this all together. What are the key takeaways when it comes to integrating molecular insights like KIT D816V into treatment decisions for systemic mastocytosis?

Dr. Pongdee:
Yeah, I would say one thing for sure is the diagnostic evaluation. If you're considering systemic mastocytosis as a potential diagnosis, you have to check for this mutation because, again, it's present in approximately 90 to 95 percent of individuals with the disease, and now we have very sensitive methods to look for this mutation in the peripheral blood. Specifically, we recommend what's called the droplet digital PCR technique. So if you're looking for this mutation in peripheral blood, it has to be a high-sensitivity assay; otherwise you may miss it. So that is considered a key part of the diagnostic process.

I will say also on the flip side, if you do not find a mutation, that does not rule out mastocytosis because some individuals think, 'well if they don't have the mutation, then they must not have the disease.' And while if you play the odds, I would agree that it becomes less likely, but it's not an absolute. So if your suspicion is very high, despite a negative peripheral blood test, bone marrow biopsy is still considered the diagnostic procedure of choice.

Now, when you go into treatment, knowing the presence of that is quite helpful because, again, all the clinical trials to date look for that particular mutation, and since we have targeted therapy, it makes intuitive sense that you're going after this particular mutation because if we can eliminate it, we eliminate mast cells and, consequently, we should eliminate symptoms. But again, it's important to remember that even in patients who tested negative for the mutation, they may still respond to targeted therapy. So I would not use it again as an absolute to say whether or not you should choose targeted therapy. At this point, all the trials have shown that even patients who test negative for that specific mutation still respond to targeted therapy.

And again, these patients likely have another form of the mutation that was just not assessed for. But in general, having a mutated KIT receptor is the root cause of the disease, and targeted therapy can be a very effective way to treat that.

Dr. McDonough:
As those key takeaways bring us to the end of today's program, I want to thank my guest, Dr. Thanai Pongdee, for joining me to discuss the role of KIT D816V in guiding treatment decisions in systemic mastocytosis. Dr. Pongdee, it was great having you on the program.

Dr. Pongdee:
It was a pleasure to be here today. I appreciate the opportunity, and I hope we can speak more about this in the future.

Announcer:
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