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Advances in ISM Care: Novel Therapies for Reduced Disease Burden

Announcer:
You're listening *Project Oncology* on ReachMD, and this episode is sponsored by Blueprint Medicines. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss the latest therapeutic advances for our patients with indolent systemic mastocytosis, or ISM for short, is Dr. Cela Ustun. Not only is he a Professor in the Department of Internal Medicine, but he's also the Coleman Foundation Chair of Blood and Bone Marrow Transplant and Section Chief of Bone Marrow and Stem Cell Transplant at Rush University Medical Center in Chicago. Dr. Ustun, it's great to have you with us here today.

Dr. Ustun:
Thank you. It's my pleasure.

Dr. Turck:
Well, to start us off, what is ISM? And what are some common challenges clinicians face when caring for patients?

Dr. Ustun:
ISM is a benign disease, a neoplasm of mast cells. It's a chronic disease, and unfortunately, the diagnosis is very complicated and may be delayed for 4 or 5 years, and patients may be visiting multiple doctors before the diagnosis. And it comes with multiple symptoms, and none of the symptoms are very specific.

Dr. Turck:
And as a follow-up to that, would you tell us what the difference is between controlled and uncontrolled symptom management and how we know when we need to modify therapy?

Dr. Ustun:
In ISM, symptom burden in most patients is really high. Most patients have multiple organ symptoms that are generally chronic. Are there patient groups that may have small amounts of symptoms? Yes. But the vast majority suffers from a lot of symptoms. As I mentioned before, the diagnosis is difficult because symptoms affect multiple organs, including GI tract system, cardiac functions, skin-related reactions, hypersensitivity reactions, allergic reactions, and some constitutional symptoms, like fatigue, bone pain, and joint pain. Anxiety or brain fog affects their life and work, and some patients may impair because of the disease and cannot function anymore. Daily life can be significantly affected.

Dr. Turck:
Well, with all that in mind, let's turn our attention to the evolving treatment landscape. How are newer therapies helping us address the challenges you were just discussing?

Dr. Ustun:
Well, before the current therapy options, I will say the KIT inhibitors really revolutionized the treatment of mastocytosis. These drugs are different than the classic drugs that we have been using for decades. I describe this to my patients as the antihistaminic H1 blockers or H2 blockers—generally both of them are used—mast cell stabilizers, like cromolyn, pain medications, and some leukotriene inhibitors. And these are classical drugs, and in some cases, I don't use this much, but steroids. I will tell my patients this is kind of a band-aid; you have the symptoms because of histamine, and you use antihistaminic, but you don't really deal with the root of the problem. The

problem is the mast cells.

How do we manage mast cells better than just these classical symptom-oriented medications? KIT inhibitors were approved 1 to 1.5 years ago. And these drugs, namely avapritinib, blocks the KIT D816V mutation, and therefore, the cells stop growing and start dying. And as a result of it, the mast cell burden decreases. And the studies really clearly show that in patients who receive these effective KIT inhibitors, their mast cells die and burden decreases. For example, serum tryptase goes from 50 to 25 in weeks; it's quite fast. Bone marrow mast cells go down, and spleen and liver size shrink. So it's highly effective because it directly kills neoplastic mast cells.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Cela Ustun about the latest advances in the treatment of indolent systemic mastocytosis, or ISM.

So, Dr. Ustun, you had mentioned KIT mutations just a little bit earlier, and I'd like to zero in specifically on recent strategies that target the KIT D816V mutation. What do we know about this as an underlying driver of ISM? And how does it influence our therapeutic approach?

Dr. Ustun:
It's very important in treatment. When I started to take an interest in mastocytosis about two decades ago, the mutation was known, but the frequency was not known because as medicine and molecular techniques have developed, more sensitive techniques came, and the incidence of KIT D816V mutation really increased. And today, I expect 95 percent of indolent systemic mastocytosis patients should be positive. If it is not positive, I will stop, and I will be very cautious because it comes with the disease, almost. It was known that this is a driver mutation, as you mentioned, and it makes the cells grow and gives them survival advantage without any normal control mechanisms, and therefore, the mast cells continue to grow. Two decades ago, we started using medications from other tyrosine kinase receptors; kinase inhibitors were tried and failed because they were not sensitive or specific for KIT inhibition. They were not effectively blocking the KIT. And it was disappointing. And over years, one or another failed, and then midostaurin came for the advanced systemic mastocytosis and showed significant improvement that brought attention to these drugs much more because there was an FDA-approved drug even in advanced the state. Then avapritinib came and other KIT inhibitors are currently in studies in the same field.

Dr. Turck:
Now in addition to these evolving therapeutic strategies, would you share some other best practices for minimizing symptom burden and improving outcomes?

Dr. Ustun:
Yeah, it's a very good question. Most patients have multiple symptoms, and most of them are very intelligent and know how to handle symptoms, and they pay attention to what brings the symptoms up and they try to avoid that. For example, if it is some certain food type, they don't eat it. Some alcohol ingestion is causing, for example, flushes or rash or diarrhea, they eliminate it. Unfortunately, the classical, the standard therapies, antihistaminics, leukotriene inhibitors, or cromolyn sodium, have limited activity. And therefore, these drugs that the FDA approved, mainly the KIT inhibitors, came to the attention and were approved.

When I start KIT inhibitor with my patient, the symptom burden is very important. Obviously, they have to have high symptom burden, not responsive or controlled by this, at least two medication types. In that condition, they should start KIT inhibitor because of side effects profile, etc., needs to be discussed with the patients.

Dr. Turck:
And before we close, Dr. Ustun, are there any final thoughts you'd like to share about the recent advances in ISM care?

Dr. Ustun:
I think the most important one is really KIT inhibitors make dramatic changes to me in a patient's life. I discuss with my patients if patient system burden is still high despite the classical therapies to medications and if I am convinced that I'm going to use a KIT inhibitor, I tell them this is really very exciting moment because they have had multiple symptoms and most of them were not very well controlled until then. And I say when we use this medication, now you have a chance to really understand what type of symptoms you have had for many years and what were caused by or contributed by mast cells. And once we drop them or kill them and reduce your mast cell burden, which ones are going to get better? It's trial and learning. It's learning about your body and about your symptoms that you have had for many, many years. Perhaps they didn't realize they had the symptoms because they have carried the symptoms for many decades and all of us get used to it and find a way to adjust to symptoms over time and when they start using medications and the symptom goes away, and then, 'Oh, I did have this symptom. I just realized now, because I was living every day, and I was thinking it was normal.'

Dr. Turck:
Well, with those final thoughts in mind, I want to thank my guest, Dr. Cela Ustun, for joining me to discuss the evolving treatment landscape for indolent systemic mastocytosis. Dr. Ustun, it was great having you on the program.

Dr. Ustun:
Thank you so much for having me.

Announcer:
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