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Changing the Treatment Paradigm: Taking a Targeted Approach to Treating Non-Advanced Systemic Mastocytosis

Announcer:
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Dr. Castells:
Hi everybody, I'm Mariana Castells. I'm the Director of the Mastocytosis Center, here at the Brigham and Women's Hospital. I'm delighted to be here with you, and this is going to be a conversation with our associate director, Dr. Giannetti

Dr. Giannetti:
Yeah. Hi everybody. My name is Matt Giannetti. I'm the Associate Director of the Mastocytosis Center, and I'm here with Dr. Castells, to talk a little bit about indolent systemic mastocytosis, and the therapy of this. It's my pleasure to be here.

Dr. Castells:
So I will start with indicating that an early diagnosis is critical to all patients with mastocytosis. As we have described in our previous presentations, patients can present with symptoms of flushing, of itching, of gastrointestinal pain, of diarrhea, for many years, up to 55 years in some studies, without a clear diagnosis. And having a tryptase level, having a kidney KIT D816V mutation, is critical to those patients for an early diagnosis, and potentially for management and treatment options that will increase the quality of life.

So, we recommend that all the providers that have patients who present with more than one organ system, with multiorgan system symptoms, that are compatible with myosin activation, we're providing them with a tryptase level, potentially kidney mutation, and if those are positive, going directly to a bone marrow or a tissue biopsy, subcutaneous biopsy, to be able to provide a diagnosis, and to advance the treatment of those patients.

Dr. Giannetti:
Yeah, so fantastic. I would like to transition a little bit, and talk a bit about the therapy for mastocytosis. So obviously, diagnosis is kind of the first point. You need to have an accurate diagnosis before moving forward. With indolent systemic mastocytosis, or more specifically, the non-advanced variants. I think of therapy conceptually as follows. So kind of two major areas of treatment: One would be antimediator therapy. So this is the classic therapy that we've used for many many years, involving antihistamines, oral chromin, omalizumab, certain drugs that block mediators, or mast cell activation. The more recent therapies, the targeted tyrosine kinase inhibitors, as we mentioned them, have a direct cytotoxic effect on mast cells, and they directly reduce the mast cell burden. So this is a novel treatment strategy, because rather than blocking mediators, it involves more cytotoxicity, and actually reduces the mast cells, which is primarily the problem, in many of these patients.

As we've reviewed the targeted tyrosine kinase inhibitors still are in their infancy. Many of these medications are currently in clinical trials. There are some approved for the more advanced variants, but for indolent systemic, most of them are currently in clinical trials. Let's talk a little bit about patients who would be ideal for starting these medications. I would punt it back to Dr. Castells to mention

some of the patients who she would consider for targeted tyrosine kinase inhibitor.

Dr. Castells:
Thank you so much, Matt. Yes, I do think that we are entering a new era for the treatment of patients with systemic mastocytosis, and particularly the indolent systemic mastocytosis. Those patients have been presenting to us with multiorgan symptoms, as I was mentioning. They have flushing, they have itching. The skin symptoms are very prominent. We have antihistamines, we have leukotriene blockers. And in some patients, those medications are sufficient, to to actually appease those symptoms. We do have also, pretty severe gastrointestinal symptoms. So there is a wide array of symptoms, that go from gastroesophageal reflux, to severe diarrhea. And we have also, neuropsychiatric symptoms, that show memory span, inability to concentrate, headaches, and multiple other symptoms. And most importantly, we have patients who present anaphylaxis. And that is a very, very important symptom of mastocytosis.

So, what mastocytosis is, is actually really a kind of wide range of presentations. It is not just one disease. We have some patients who present hamunaptra anaphylaxis, and they only have symptoms at the time of hamunaptra stings. And we have patients who present with daily symptoms of mast cell disorders, based on their mediators. So again, we don't have enough understanding about all the presentations, and the biomarkers of the disease. And we have patients who we have treated for 30 years, with few medications they have done well. And on the other hand, we have patients who we have treated, with the most upgraded medications, including omalizumab, and IgE, and they continue to have symptoms. So when do we qualify patients for the next level, are the patients that are not controlled, are patients who have poor quality of life, are patients who have daily symptoms, are patients who actually have impaired activities, whether professional, familial, social activities, that are actually impaired.
They cannot get out of their houses, they don't know when they will have diarrhea next. Patients who constantly itch, that wake up in the middle of the night. So again, the indolent systemic mastocytosis, even if it's one just category of mastocytosis, it has an array of presentations. And the patients, for whom, despite the best treatment, best options, best medications, are not under control, are the ones that we consider to be the next level for targeted therapies.

I also want to add the caveat, that there are patients who have cutaneous mastocytosis, whether adolescents, children or adults, in which we really don't have any actually targeted therapy. And although we have made our tremendous effort to target the therapies for mastocytosis, in the line looking at that KIT, which you know in 95% of the patients is mutated, and D816v, in those patients with cutaneous mastocytosis, some of them will have that mutation. Some of them we don't know what mutation that would have. But we are not at the present time targeting those patients. So I would like to ask Dr. Giannetti, you know, what are the kind of the approach that you will do with those patients, who actually are not under control, with the best care and best medications?

Dr. Giannetti:
Yeah, fantastic explanation. So I agree completely. This particular patient group, has a wide variety of presentations. And the ones who are really not doing well, despite best available therapy, are really the patients that I like to try and targeted tyrosine kinase inhibitors. So yeah, my approach to these patients, while generally starting with the substrate of somebody who's been maximized on all available medications, and despite this, is not doing quite well, this is somebody who I would consider for a targeted tyrosine kinase inhibitor. I think at present, it's a little bit challenging, because we do not actually have any of these medications that are FDA-approved for routine use.

So, you know, the current advice would probably be referring some of these patients to a center of expertise, whereas they have the availability for clinical trials. For our patients here, we're an active site, enrolling many patients. So I have quite a low threshold to put these patients on targeted tyrosine kinase inhibitor therapy, primarily because the drugs are reasonably well tolerated and they very significantly improved quality of life, assuming that the correct patient is chosen. I wanted to also talk a bit more, about monitoring some of these patients, and looking out for side effects. Because some of these medications, not some, I mean by definition they're cytotoxic, they carry a much higher side effect profile than things such as over-the-counter antihistamines, or other more benign medications. A couple of important things to remember: So first and foremost, the side effect profile is directly related to the concentration or the dosage of the drug.

This is important, because in different forms of mastocytosis, different types of drugs have been studied. So for example, with the single molecule avapritinib, the higher dose has been used for those with advanced variants of mastocytosis, versus those with indolent systemic mastocytosis, have used a much lower dose. At the lower dose, we do generally see a better side effect profile.

Things that I have seen commonly, and things that I would clinically monitor for: One, cognitive changes. We have seen a good amount of, you know, forgetfulness, other cognitive abnormalities on these patients. We also see a good bit of swelling. So edema, it can be facial edema, it can be extremity edema, or it can be lower extremity edema. And then there's hematologic abnormalities as well. So anemias, and other cytopenia, are very important to monitor for. With that, I would like to pass it back over to Dr. Castells. She can talk

a little bit about additional side effects, and then more of the long-term implications of the medications.

Dr. Castells:
Yeah, no, those are perfect side effects, Dr. Giannetti. What I wanted to actually make a point, is how do we enroll patients for clinical trials? Because I think that that the key is here, how we actually inform patients about those clinical trials. And I think you made a really important point, about sending your patients to centers of excellence, like the Brigham, like Michigan, like Stanford, by all those centers, where clinical trials are being done at the present time.

So clinical trials are really kind of a novelty, for the treatment of systemic mastocytosis. And I think the critical point here, is the information. When a patient comes to us, and asks, "Doctor, I've been having those symptoms, "you've been treating me with the best medication, "and I continue not to be able to do things "that I would like to do," that is when we need to actually inform the patients that clinical trials are available to them.

The same way that we have clinical trials for cancer, the same way we have clinical trials for chronic inflammatory disease, there is now clinical trials for rare diseases, such as mastocytosis. And so our job is to inform not only, you know, our colleagues in immunology but all the other specialties, and also tell the patients, that through Mastocytosis Society, they can actually tag along, and ask their provider, "Is there a way in which I can actually participate "in a clinical trial?" And we have been blessed here, at the Brigham Women's Mastocytosis Center.

We are a multidisciplinary center, with dermatology, gastroenterology, hematology, neurology, and all the other specialties, because mastocytosis is a disease that affects all organ systems, and we actually need to have a multidisciplinary approach to the disease. So I would say that the modern era of the treatment of mastocytosis, is a targeted approach, a molecular approach, and looking at those molecular targets, is what we need to do, in the near future. I am delighted that the next generation of allergy immunologists, such as Dr. Giannetti, are embracing, you know, the treatment of mastocytosis, and are wanting to treat those patients with the newest therapies.

Dr. Giannetti:
Great. I think that sounds fantastic. Very nice spending this time with you, Dr. Castells, and chatting about mastocytosis, and novel therapies. Thank you very much for your time.

Dr. Castells:
Thank you everybody.

Announcer:
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