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Case Challenges in Systemic Mastocytosis: Clinical Insights From the Expert Roundtable

**Announcer:**
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**Dr. Bitar:**
What is mastocytosis? It is a neoplastic disorder. It is not only increased activity of the mast cells, but also there is increase in number, and there is accumulation of those mast cells in a clone, whether in the skin – this is called cutaneous mastocytosis only – and then systemic mastocytosis where you have extracutaneous organs involved, you can have involvement in the bone marrow and the liver and the spleen, among others. You can have that without involvement of the skin. The last type is the mast cell sarcoma, which is a very rare type and usually very aggressive.

Systemic mastocytosis is definitely not the same as MCAS. We are not really going to be discussing MCAS because that is a lecture by itself. But you do have mast cell activation in systemic mastocytosis, so you can have symptoms that looks like MCAs, but really the two terminologies are not equivalent.

Pathophysiology of Mastocytosis

What happened? What is the pathophysiology of mastocytosis? You do have a stem cell factor that triggers that KIT receptor on the mast cells. In mastocytosis, there is a KIT mutation and there is a gain of function. This will lead to activation of these mast cells without really a lot of triggers, then that will lead to overactivation, and then more release of histamine, prostaglandin, among other activators. This will lead to more symptoms like itching, flushing, fatigue. You can have anaphylaxis, osteoporosis and GI as well, like abdominal pain, diarrhea. We will talk about more other symptoms involved in mastocytosis as well.

Symptom Burden of SM

Looking at the patient reported symptom, what they are bothered by mainly, it is mainly the skin related, with the flushing and itching. This is what we see a lot in our clinics, and GI. Skin and GI are really big for those patients. Anaphylaxis is the most scary one for the patients when it happens. Fatigue, exhaustion, and then you have all this spectrum of non-specific skin symptoms. And symptoms like fatigue, being depressed or brain fog or just weakness, they do not feel themselves. By itself, they do have very non-specific generalized symptoms as well.

Looking at the score here, this score looks at how the patient is feeling overall, similar to a quality of life. One is you are at your best, and then less than one, that means you are really not doing very well. As you can see here, the advanced systemic mastocytosis definitely have a lower score than in indolent systemic mastocytosis. Even overall, the patient will not be feeling very well when they have this disease.

Adult vs Pediatric Onset Mastocytosis

Adults versus pediatrics mastocytosis. This is an important distinction. We lump them into the same disease. Some people think they are a little different because of how they present and the prognosis of those two different diseases.

In adults, you do have most of the time indolent systemic mastocytosis. If you do have skin involvement, please check a bone marrow. Even if your tryptase is normal, you want to make sure that your patient does not have systemic involvement.

For peds, there is no criteria for that. Most of the time it is in the skin and remains in the skin. It starts looking more scary. It is very polymorphic. They can blister. It is definitely very scary for the parents, but usually they do well and it resolves eventually. Anaphylaxis in pediatric patients is less likely to happen compared to the adult patient, where it can happen in about 50%.

Tryptase level in adults is usually higher, more than 20. The KIT mutation, the D816V, which is the most common mutation that we talk about in mastocytosis, is more prevalent in adults. We have tons of other mutations in kids, and sometimes you do not find much. This is why people think, are these really the same family of diseases? Very monomorphic, red, orangey, brownish look on the skin for adults. They all look the same. They start on the thighs, go up to the trunk. Usually does not cross the neck. Head usually is not involved in adults, but kids actually they do have head and neck involvement and that is one of the characteristic features.

Skin Lesions of Mastocytosis

This is what we are talking about. This is the monomorphic small lesions that are typical of indolent systemic mastocytosis in adults. You can have few of them, and you can have tons of them like the initial picture. Sometimes they cause the skin to be a little darker in look. It gives a different tone than the actual skin type of the patient.

In kids, as you see, bigger lesions, they can blister, they look different in size and shapes, but they usually do actually better than the adult.

**More on Typical Cutaneous Lesions of Mastocytosis**

Again, adults, you always want to rule out indolent systemic mastocytosis. It is very rare to be only a cutaneous disease. Skin manifestation is very common in indolent systemic mastocytosis of adults. Darier's sign which we mentioned initially for our case presentation, this is when you rub the lesion, it causes more swelling. It releases all the histamines and prostaglandins and all the other markers to cause more swelling and redness of the lesion. It is usually present. Again, they start on the thigh and go up to the trunk, distal extremities and neck, and usually avoid the face for adults.

Diagnostic Algorithm for Mastocytosis

This is the diagnostic algorithm for mastocytosis. If you have a suspicion of mast cell symptoms and you have anaphylaxis and you have some elevated serum tryptase, or if you do have adult onset skin mastocytosis biopsy-proven, then those patients need to have evaluation for more systemic disease – so biopsy, bone marrow and all other involved organs – and then you want to really do that molecular testing of the KIT D816V. It is best done in the bone marrow and the blood, but you can do it on the skin as well. It is not as accurate, however.

Mast cell immunophenotyping in the bone marrow in particular, and then you want to screen for the main mutation, which is the KIT. If it is negative you can screen for this other mutation which is FIP1L1::PDGFRA, and then you can look for eosinophilia if it is present.

Diagnostic Criteria for Systemic Mastocytosis

Diagnostic criteria, we do have major and minor criteria. The WHO classification needs one major and one minor criteria, or more than three minor criteria. The international consensus is a little more loose with one major criteria and more than three minor criteria. Again, major criteria, you need to have multifocal dense aggregates of mast cells, more than 15 in the bone marrow and/or extracutaneous organs. The minor criteria, you need more than 25% of the mast cells to be of atypical morphology. Usually, they are round under the microscope, but what they mean by atypical morphology, they become more spindly, more elongated, and then they have the aberrant expression of CD2, CD25, and/or CD30 expression on the mast cells. This is again done in the bone marrow. I do not usually do those on the skin, they are not very relevant. KIT D816V mutation in the bone marrow or like on the skin could be done as well, and then the serum tryptase more than 20 in the absence of any other myeloid neoplasm.

Why this is important, because if you do have another myeloid neoplasm, you can have high tryptase, and that might be completely different. It does not need to meet the criteria.

Identifying Systemic Mastocytosis Subtypes

This is the gist of what we talked about in our question. There are multiple subtypes. What we see mainly is that indolent systemic

mastocytosis, which is the most common presentation. Typically, they have skin lesions. They usually are non-advanced, but they do have significant skin lesions. Usually, they do not have a lot of other involvement other than just the bone marrow. The tryptase would be more than 125, and then usually less than one of the B-findings, meaning the systemic mastocytosis burden, so hepatosplenomegaly, lymphadenopathy, all of that. The patient is not super sick, but they are definitely having symptoms and mainly skin symptoms.

The bone marrow mastocytosis. That is a tricky one. A lot of you thought about that on our case, but usually they do not have skin lesions. This is a very important distinction between the bone marrow mastocytosis and the indolent systemic mastocytosis. Both of them are not advanced. The bone marrow mastocytosis really does not have B or C-findings. It is brewing in the bone marrow, but still, it did not really release itself yet.

Smoldering systemic mastocytosis, you do not have a lot of skin lesions, and then you do have more B-findings, so hepatosplenomegaly, cytopenia, lymphadenopathy. You do not have any C-findings where you have organ damage, and then you do have the more advanced one associated with hematologic neoplasm. This will follow that specific hematologic neoplasm criteria. Or you have the aggressive systemic mastocytosis where you have damage with involvement of this mast cell infiltration of the organ, and then you will have more severe symptoms.

The MC leukemia, as we mentioned before, is a very rare finding where you have more than 20% in the bone marrow and then in the blood as well, so more circulating.

The other thing I want you to think about, whenever it becomes more internal, they lose their skin lesions and everything becomes more in the blood and the other organs.

Differential Diagnosis

The differential diagnosis is very wide. You do have the mast cell activation syndrome that we just mentioned, you have idiopathic or monoclonal, and then you have patients that have anaphylaxis or angioedema. You also have the other dermatological problems that could look like flushing, itching: chronic spontaneous urticaria, atopic dermatitis, rosacea. You have endocrine, so definitely you want to check their thyroid, you want to look for carcinoid syndrome. You want to make sure with all their GI symptoms like IBDs or IBS. And then again, neurologic. That is a big one. They have headaches, seizures, strokes, dysautonomia. Then again, the psychological: anxiety, panic attacks, depression. A lot of ruling out while you are doing your diagnosis. A very good history and review of system would help you a lot on that case.

Posttest Question 1

We are back to our post-test question. Julian, again, is a 36-year-old man with a history of spreading, small lesions on the skin, who received testing for systemic mastocytosis. His findings included a KIT mutation that is positive, serum tryptase of 48, and a dense multifocal bone marrow mast cell aggregates. Based on these findings, which systemic mastocytosis subtype he is most likely presenting with?

A. Indolent systemic mastocytosis.
B. Bone marrow systemic mastocytosis.
C. Smoldering systemic mastocytosis.
D. Aggressive type systemic mastocytosis.

Let us see the polling. Okay, that is great. We do have more voting for the indolent systemic mastocytosis, which is the accurate diagnosis. Again, the difference between this and the bone marrow one is that skin involvement that is very prominent for indolent systemic mastocytosis. This patient presenting with these red lesions, and he has a positive Darier's sign. Just remember, you definitely need to do a skin biopsy to confirm skin mastocytosis. These criteria on having KIT mutation, having the tryptase, and having the bone marrow infiltrate and the skin lesion will make him fit the criteria for indolent systemic mastocytosis.

This is what we were just discussing. WHO guidelines again, systemic mastocytosis, KIT mutation, high tryptase, and then dense multifocal infiltrate. He has one B-finding, then the bone marrow, that is the one that was very tricky for you all. The bone marrow in particular does not have a lot of skin lesions compared to the indolent systemic mastocytosis.

Case 1: Q&A

I am going to see if we have some questions here. We have one. When you see B or C findings, how does that shape prognosis or follow-up discussion with patients?

That is an excellent question. First, if we do have these findings, and then we have referred to our colleagues in hematology-oncology,

and then they did the bone marrow, and allergy immunology, and then they have started the treatment, it is important for us to see the patient in clinic closely and follow up on the skin symptoms as well. They usually do really well when they start their treatment with their organ involvement, but sometimes the skin lags behind. Dr. Giannetti is going to talk a little bit more about treatment. This is important for us because we do have some modalities that help, but unfortunately, sometimes we cannot really control their skin the way that the patient is expecting. If they do have the B and C-findings, that means more close follow up on those patients to make sure they are not going into more advanced stages.

# Targeted Therapies for Systemic Mastocytosis

I am going to hand it to Dr. Giannetti to talk about more therapies for systemic mastocytosis.

**Dr. Giannetti:**
Thank you, Dr. Bitar. I would say that question dovetails quite nicely into my section here; targeted therapies for systemic mastocytosis. Typically, if you have B or C findings, it does represent a more aggressive disease, so oftentimes, we are talking about some of the tyrosine kinase inhibitors.

Patient Case 2: Darren, 44-Yr-Old Man

With that said, let us start off with a case report here. This is Darren. He is a 44-year-old man with a two-year history of known indolent systemic mastocytosis. He was referred to dermatology after developing persistent itchy reddish-brown lesions on his torso. These spots, as typical with cutaneous mastocytosis, worsened with heat and friction. He is here because he basically wants to discuss treatment options that may work to improve quality of life and improve his lesions.

Briefly on his past medical history, he is had a couple of prior episodes of presyncope. He is on cetirizine and montelukast.

In his laboratory findings, he does have the KIT D816V mutation. He does not have any other non-KIT mutations on a myeloid NGS. That is an important finding here. His tryptase is 58 nanograms per milliliter. He has dense mast cell aggregates in the bone marrow biopsy. You can see right there that is a major criteria and two minor criteria for systemic mastocytosis.

Pretest Question 2

For Darren, indolent systemic mastocytosis with KIT mutation. We went through his information here. For six months, a combination of anti-mediator therapies improved itching and diarrhea, but there was little improvement in his cutaneous lesions. Based on the PIONEER trial, which statement would be correct when discussing the impact of avapritinib on his symptoms? I will not go ahead and read A, B, C, D here for you. I will let everybody read it themselves. But why don't we pause for a minute, let you read and answer the question?

It looks like most people answered B. Avapritinib improved skin lesions when used in combination with topical corticosteroids. Let us go through the teaching section here, and we will bring it back to answer this question more definitively.

Treatment for Mast Cell Mediator–Related Symptoms

When I think about treatment of mast cell mediator-related symptoms and treatment of mastocytosis in general, I think of two defined pathways. The first pathway is going to be the tried and true mediator-related symptoms. Typically, antihistamines, leukotriene receptor antagonists, etc. The second pathway is going to be tyrosine kinase inhibitors. Let us spend a slide or two here focusing on the mediator-related symptoms.

Subdividing this further, when I think of mediator-related symptoms, I think of a targeted organ therapy effect. Skin here. Lots of itching, hives, flushing, angioedema. Typically, H1 and H2 are the first-line therapies. In my clinic, at least, I like cetirizine 10 milligrams twice daily, and often famotidine 20mg twice daily as an initial start, and then up-titrating, down-titrating from there. Alternative options, I use quite a bit of montelukast. We can use aspirin, ketotifen, topical cromolyn. I use less topical cromolyn. I think oral cromolyn is a little bit better, but all of these are viable options.

GI symptoms are probably the second most common grouping of symptoms in mastocytosis. I lean quite a bit on H2 antagonists, so famotidine, cromolyn can be quite helpful, as can PPIs. As it turns out, histamine can directly activate the parietal cells of the stomach and small intestine. Histamine oversecretion or overproduction from mast cells leads to acid hypersecretion. Gastrointestinal reflux disease, and reflux in general, is much more common in patients with mastocytosis.

As you can see here, going down the list, in all of these organ systems, we typically use H1 and H2 as a first-line therapy for really

everything. A couple of specific call-outs I would like here. For cardiovascular, you see presyncope and tachycardia. This is most typically in the setting of anaphylaxis. I am an immunologist by training here, and we use quite a bit of omalizumab for things like this. It works phenomenally well for anaphylaxis. For patients with intermittent hypotension, presyncope, etc., I would strongly encourage you to get them over to immunology so we can use omalizumab.

Occasionally, we will use corticosteroids, both inhaled for the lungs and more commonly topical, even systemic, for acute flares.

Other Therapies for SM

Moving forward here, a couple of other systemic therapies for systemic mastocytosis. Two medications we use occasionally. Imatinib has been tried and true for many years. A couple of really important points about imatinib. The D816V mutation is resistant to imatinib. It is critical that you have good documentation on D816V. What that typically means is checking D816V in the bone marrow or bone marrow aspirate. D816V negative in peripheral blood does not definitively exclude that mutation in any human. Typically, these are at quite low burdens. Mast cells do not really circulate through peripheral blood. They live in the bone marrow, so you really need a bone marrow aspirate to definitively ensure people do not have the KIT D816V mutation.

This is really important because, probably once or twice a year, I will get referrals for D816V-negative patients who are not responding to imatinib. Typically, we have missed a low burden D816V, so patients will not get better with imatinib if they have D816V.

Midostaurin is approved for more advanced systemic mastocytosis, so aggressive SM and the more oncologic indications of SM. It is not currently approved for indolent systemic SM. This medication is a multikinase inhibitor. It has two approvals for advanced SM and for FLT3-positive AML. It works quite well in aggressive disease, but has a lot of side effects. For many years, the quest has been to narrow the targeting of these medications to really improve the side effect profile.

KIT Mutations as Drivers of Systemic Mastocytosis

Moving forward, here I want to touch base a little bit on KIT mutation. The ongoing thought in systemic mastocytosis is that basically all patients have some activating KIT mutation. We see KIT D816V as by far the most common KIT mutation. Depending on a series of literature, it is in 85 to 95% of humans. There have been many other activating KIT mutations that have been reported, but KIT D816V is by far the most common.

What does the KIT D816V or other activating mutations do? If you take a look at this figure here, you see KIT. KIT is an extracellular tyrosine kinase receptor or RTK, receptor tyrosine kinase. Its ligand here is SCF. Dr. Bitar mentioned it a little bit earlier, stem cell factor. What happens is stem cell factor will come to the KIT, KIT dimerizes, and then sends a signal intracellularly. You can see here phosphorylates, ATP, ADP. This goes on and initiates a stream of events in the mast cell.

KIT D816V is right here in the active kinase domain, and it causes it to be constitutively active. What happens in the presence of D816V is you lose the ligand activation. The tyrosine kinase is constitutively active. This drives proliferation, it drives survival, and it drives maturation of the mast cells, too. We do not have it listed here but it also changes the activation threshold. These mast cells tend to be a little bit more wobbly and a little bit more likely to activate as opposed to wild-type native mast cells.

Targeted Therapy in Systemic Mastocytosis

Moving on to the main purpose of this section, targeted therapy in systemic mastocytosis. A little bit of a busy slide here, but in indolent systemic mastocytosis, I want you to think of the mast cell as a whole unit here. This is a nicely drawn mast cell, nice circular nuclei, lots of granules in there. Mast cells have really a boatload of ways that it can be activated. We see complement receptors. We can have IgG, we see IgE. Regardless of the motivation or the modality of activation, these cells will release a variety of chemicals; so tryptase, we think of histamine, leukotrienes, prostaglandins, and a bunch of cytokines. I want to call particular attention to the KIT protein and specifically KIT D816V. You see avapritinib blocks right here, intracellularly in the KIT D816V mutation, and more or less starves the mast cell. It also decreases activation a little bit, but more importantly, it leads to cell death of mast cells.

The purpose here is that all of these symptoms at the bottom can be triggered by mast cell activation. All the symptoms we talked about before. The central thought with the tyrosine kinase inhibitors is that if you remove the mast cells, you do not need to block the mediators because the cells that are producing the mediators are no longer present. That is the overarching theory with our targeted tyrosine kinase inhibitors.

PIONEER: Efficacy of Avapritinib vs Placebo in ISM

Moving forward on these medications, I want to talk a little bit about the seminal trial that led to the approval of this medication. This was termed the PIONEER trial. It was published in *New England Journal of Medicine Evidence*. Avapritinib versus placebo in indolent systemic mastocytosis.

There are a couple of important things about entry into this trial. One, patients had to have moderate to severe indolent systemic mastocytosis symptoms. This was gauged by what we call the TSS or total symptom score. It was basically a compendium of symptoms across multiple organ systems. Are you itchy? Do you have flushing? For skin symptoms. For GI; do you have diarrhea? Do you have bloating? Constitutional symptoms; do you have fatigue? Are you sleeping too much?

We took this combination of symptoms and basically asked patients to rate on a daily basis what their scores were and we came up with an aggregate score. The maximum of this is 44, I think, and in order to enter into the trial, you had to have at least greater than 28 uncontrolled symptoms despite greater than two anti-mediator drugs. Typically, this would include H1 and H2 antagonists. If you were still symptomatic despite these medications, you could enter into the trial.

Looking in a little bit more detail, what did avapritinib do? You can see here a comparison against placebo. Avapritinib is the reddish orange graph or bar. The grey bar is placebo. How we measure this, this is more, I would say, oncology-style trial reporting. We are looking at people who had greater than 50% reduction in all of the following mediators. You can see here a total symptom score. Avapritinib patients were much more likely to have greater than 50% reduction in TSS compared to placebo. You can see really for all of the questions, so for serum tryptase, for KIT D816V VAF, variant allele fraction, and for the bone marrow mast cell burden, significantly more patients reached a greater than 50% reduction on avapritinib versus placebo.

PIONEER: Cutaneous Findings with Avapritinib in ISM

Focusing a little bit more on the skin here. Skin biopsies were required for all patients with skin lesions in the study, so all of them underwent skin biopsy prior to starting medication and six months after starting medication. We used both the skin lesions and there was also skin photography, which was able to measure the assessment of body surface area involved, the change in pigmentation and the resolution of cutaneous lesions. Using these two metrics, we can look here at change in skin lesion area at 24 weeks. That is roughly the six-month time point that I was talking about.

Again, same color scheme here as present. Avapritinib is in the reddish orange and placebo is in the grey. You can see really across the board focusing on different areas of the body, in all situations, avapritinib has a greater percent change from baseline, a greater reduction in skin lesion areas compared to placebo. This holds true for the thigh, for the torso, for the front of the thigh, the front of the torso, and then the most affected area.

I would say mastocytosis is a disease that involves many organ systems, but skin is the most visible organ. These skin lesions really bother people and really impair their quality of life. This represents a significant improvement in quality of life for most of these patients. Very encouraging findings.

PIONEER: Long-term Improvements in QoL and Symptoms with Avapritinib in ISM

Moving forward, many things that we care about in oncology-related diseases are long term stability and long-term improvement. It is great that we improve people's quality of life and reduce their symptom burden, but it is equally important to show that that is maintained over a period of time. This is what this slide here attempts to address. We are looking here again at the Total Symptom Score, TSS score, at 96 weeks, so roughly two years, and 144 weeks, roughly three years of avapritinib exposure. Again, what we are looking for is maintenance of symptom improvement.

In fact, as it turns out, you can see avapritinib at 96 versus 144 weeks, not only there is maintenance and symptom improvement, there is a deepening of symptom improvement. This holds true up through three years of medication.

This was actually just published too. I just got an email earlier today that it went live on *PubMed.* If you are more interested in this, go pull up *PubMed.* There is a bunch of us who are all authors of it here.

Moving to the second one, individual symptom domain scores. If we fragment the total symptom scores into particular domain, so GI, skin, neurocognitive, the same holds true. Looking at three years, not only do people maintain their symptom improvement, but in fact it deepens in all three domains.

Finally, in the quality-of-life score. This is spatially separate from the TSS score, but it is another scoring system that we use more generally to measure quality of life, more along the lines of how often do you avoid doing things that you enjoy doing because of mastocytosis? How often do you have anxiety about going into large rooms or worry about where is the bathroom, etc.? Again, in this, patients improve over the course of two years and that symptom improvement is sustained and in fact heightened over the course of three years.

Avapritinib: Warnings, Precautions, and Common AEs

Moving forward a little bit, avapritinib's warning precautions and common adverse effects. The one that patients will always ask about is

going to be intracranial hemorrhage. We have seen this. They have been exclusively isolated to patients with advanced variants of the disease at high doses of avapritinib. Really important to note here, I try to walk people off the edge of the cliff, if you will, in my clinic, when they read about this. A couple of points that I would say.

One, we have never seen any bleed worldwide in any human with indolent systemic mastocytosis. Full stop. Two, we have never seen a bleed at doses of 100mg or below. Typically, what is FDA-approved is 25, although many people will use 50. Regardless of those doses, at the ISM dose, it is well below any dose that we have seen a bleed on.

Some of the effects that are actually more tangible and we do see cognitive effects, avapritinib does cross the blood-brain barrier. From time to time, I will see people who have forgetfulness, medical memory difficulties, etc. We see a little bit of phototoxicity as well. Maybe most importantly here on the right, embryo-fetal toxicity. Avapritinib, as with all other tyrosine kinase inhibitors, are teratogenic. People cannot get pregnant on these medications, so birth control or two methods of reproductive potential is really important for these medications.

Investigational Selective KIT Inhibitors

Avapritinib is not the only one. It is currently the only FDA approved targeted tyrosine kinase inhibitor. There are two others that are in clinical trials. Elenestinib in the HARBOR trial is currently enrolling patients. We are currently actually on part two right now for phase II/III trial. It is a definitive trial, currently placebo controlled and currently enrolling patients.

The SUMMIT trial for bezuclastinib completed enrolment in late 2025. They just released some early publications on it. It looks quite promising. Full data is still pending on that. That is no longer enrolling patients, and not – yet, hopefully – FDA approved. Looking at the early data that they have, you can see check marks or maybe x's across the line here. Much like avapritinib, they improve symptoms as measured by symptom scores. They reduce tryptase, reduce KIT D816V, reduce mast cell burden and have a favorable safety profile.

A really exciting time for mastocytosis. We used to have antihistamines and finger crossing. We now have an FDA-approved drug and we have hopefully more coming. Very exciting.

What I would also mention here at the bottom in the ongoing phase II Apex trial which is an advanced systemic mastocytosis, bezuclastinib also shows very promising data. It is associated with progression free survival at 82% at 24 months. Again, the advanced variants are very different diseases. The outcomes are often survival rates, which is very different in indolent systemic mastocytosis.

Other Emerging Therapies

A couple of other emerging therapies. Masitinib in phase III trial. This trial is no longer enrolling. I have not heard much. I do not think this one will pan out.

TL-895. This is a completely spatially separate medication. It is a BTK inhibitor similar to remibrutinib, which I am sure much of the dermatology audience will be familiar with. Rilzabrutinib is another BTK inhibitor approved for ITP. These medications are currently in clinical trials. There is no early data whatsoever, so exciting to see how this will pan out.

Posttest Question 2

All of that said, let us go back to our post-test question number two. Darren has indolent systemic mastocytosis with KIT D816V. I have read this, so I am going to skip over reading it. I will allow people to read again. This is the same question as before. I will be quiet for a minute and let everybody go ahead and answer the question.

Okay, excellent. Avapritinib improved mast cell burden and reduced lesion surface area. Most people got it right. Let us advance the slide here and we can chat a little bit. D is the correct answer.

Results from the PIONEER trial, which we just talked about, show significant improvements in mast cell burden across multiple areas – skin and bone marrow were the two pieces of data that I showed you – and reductions in skin lesion surface area located in all areas assessed across the skin. Yes, D here is the correct answer.

Case 2: Q&A

Question and answer. Looks like a question here. What patients would be the best candidates for avapritinib?

Good question. It depends. In my clinic, it is one of two reasons. The primary reason is patients who are really quite symptomatic despite control or despite maximal medication or at least a handful of anti-mediator therapies. There are a lot of people out there who are on cetirizine, who are on famotidine, even those who are on omalizumab, montelukast. Despite all of our best efforts with quite a bit of polypharmacy, often they are still quite symptomatic. In those patients, particularly when their tryptase is elevated, avapritinib often

enormously improves the quality of their life. That is one.

I would say two is patients with a little bit more aggressive type disease. These are patients with very high mast cell burden. High baseline serum tryptase, significant involvement in bone marrow, high KIT D816V variant allele fractions. When we see these things, generally we know that there is a little bit more risk involved in this disease. I tend to put those patients on avapritinib maybe sooner, even if they are only moderately symptomatic.

I have one more question here. I think I have one minute. How long can you use avapritinib in kids and adults safely?

This is a good question. I think one of the main downsides of avapritinib, we do not really have an off-ramp at this time. I think of this disease as a much earlier version of something like CML. In CML, the oncologists will treat with tyrosine kinase inhibitors for typically five years, sometimes more or less depending on the specific context. Then they pause therapy, and they can often observe. We do not have sensitive enough tools yet. Mast cells do not live in peripheral blood, so we are quite a bit behind them. But in general, the conversation that I have with my patients right now is that once you initiate avapritinib, you will be on this over the long term. I do think this is changing as we have more potent, more targeted tyrosine kinase inhibitors that appear to lead to deeper recession, but for now, it is an open-ended question and I would say long term.

With that, I will be quiet here and hand it over to Dr. Ungar.

# Centering Patients in Long-term Systemic Mastocytosis Care

**Dr. Ungar:**
Thank you very much. Good evening, everyone. I am going to discuss the section of Centering Patients in Long-term Systemic Mastocytosis Care.

Patient Case 3: Margo, 55-Yr-Old Woman

As before, we are going to start with a case. Margo has a three-year history of indolent systemic mastocytosis. She presents to dermatology for a check-up. Her cutaneous disease is stable. She is experiencing some flushing and increased itching. Margo reports challenges with managing her lifestyle triggers and is concerned about how systemic mastocytosis affects her daily life. She has a history of anaphylaxis caused by a bee sting two years prior, osteopenia, hypertension, and hyperlipidemia.

Pretest Question 3

We will start off with a question and then jump into the meat of this.

Which of the following strategies would you recommend for Margo to prevent any life-threatening reactions caused by her indolent systemic mastocytosis?

A. Limit physical exertion to prevent future attacks.
B. Prescribe an antihistamine to use on demand in case of an allergic reaction.
C. Carry an epinephrine autoinjector in case of future anaphylactic events.
D. Trial an elimination diet to reduce dietary triggers.

We will give everyone a moment to answer that. All right. The majority of people picked C, carry an epinephrine autoinjector in case of future anaphylactic events.

Living With Mast Cell Diseases

There are a couple of trends that I am going to be discussing. You are going to hear me repeat over and over again two in particular that I think are important. The first is that this is a multi-organ, multisystem disease and therefore requires multisystem combined and coordinated care.

The second part is helping patients to be empowered and participate in their care, and understanding what this disease means for them and how to navigate it. Those are the two overarching trends. Because this is a complicated condition, symptoms are often not so specific. It is very possible that patients have not been able to identify always what is going on with themselves. Maybe they have seen providers who have been dismissive, as can be the case with conditions that have very vague multisystem symptoms. I am a dermatologist. Dermatologists are not necessarily always going to be the primary focus or the point person for treating this, but we can play an important role in making sure that we really establish that dialogue with patients and ensure that they are seeing the specialist

that they need to.

With mast cell diseases, one of the roles that we can play is educating patients on what is going on from a pathophysiologic perspective high level, but also what that means on a daily basis. Knowing their triggers. It may very well be that they have identified some themselves, but nevertheless avoiding allergens, stress – easier said than done often to manage stress, but that can certainly play a role. Be aware of triggers like temperature changes, and carry epinephrine at all times, which we will return to as well.

Common Triggers in Systemic Mastocytosis

Common triggers in systemic mastocytosis. Again, patients will often identify some of these, but nevertheless helps to make it a little more clear-cut. Temperature changes or extremes, stress, fatigue, certain foods and beverages, medications, infection, Hymenoptera venom – that is, bees, wasps, stinging insects, surgeries and procedures. Again, much of the role that we can play is empowering and educating patients so that they know in advance how to handle things as they come up.

Considerations for SM Management

Whenever possible, referral to a specialized center for systemic mastocytosis management is recommended because this is complicated, and in an ideal world, people who really focus on this are going to take the lead. Now, that is not always possible, so it is also important to understand some of the immediate steps and to know who to connect patients with, even if it is not at a specialized center.

Baseline DEXA scan is recommended. If you feel comfortable doing that, great. If not, ensure that they are connected with someone who can order and interpret the results. Patients with systemic mastocytosis are at high risk for osteoporosis, bone fractures, in particular vertebral fractures. Getting that baseline is important to diagnose them and also track over time.

We talked about counseling, advising patients to avoid known triggers. In particular, as we will see, the venom, the Hymenoptera, spider, and all that. That is a very high-risk factor for anaphylaxis. Certainly, it is important that we make sure that they have autoinjectors of epinephrine because they are at very high risk for anaphylaxis. Having that plan in place before they experience anaphylaxis certainly is key.

Ultimately, navigate and assess over time what their symptom burden is, what the quality-of-life impact is, because so many of the symptoms are nebulous and diffuse or intermittent, and sometimes what feels non-concrete, putting that all together in terms of their quality of life can be helpful.

Patient Anaphylaxis Education

We have already touched on anaphylaxis a couple of times, but it really bears repeating. This is essentially the primary life-threatening consequence, certainly immediately life-threatening consequence, of mastocytosis. The prevalence is up to 50%. This was one study that showed almost a third of people are going to the emergency room for anaphylaxis. A very nontrivial proportion have used epinephrine more than once.

When someone comes in, perhaps as a dermatologist, we are the ones diagnosing them initially. In addition to connecting all that, making sure that the patient understands what anaphylaxis looks like. People may be familiar with the term at a high level, but not the specific signs and symptoms. Access to and training on epinephrine injection and a treatment plan.

Part of this is because anaphylaxis is a very stressful, panic-inducing outcome. Things can progress rapidly. If patients do not know in advance, have a plan, do not know what to do, that is really not the time to figure it out. Having this action plan in place, having the epinephrine training is crucial, and then the symptoms as well. It is worth noting that systemic mastocytosis patients, perhaps more typically than others, experience hypotensive syncope as part of their anaphylaxis. Again, having them be aware that light-headedness may be a precursor to a more significant reaction.

Addressing SM Comorbidities: Multidisciplinary Care

Hammering home the idea of multidisciplinary care. This was one study looking at what the diagnosis and management breakdown is of systemic mastocytosis across different specialties. Perhaps not surprisingly, hematology-oncology and allergy-immunology, in many respects, taking the lead, certainly on management. Not surprisingly, dermatologists have the most disparate diagnosis to management because it may be that there are these non-specific symptoms, but they come in for the skin findings. It is relatively straightforward to biopsy, identify the mast cell infiltrates, and then ultimately get the process started on a concrete diagnosis.

That is one piece of the picture. I don't think most dermatologists are going to be treating GI symptoms, allergy symptoms, and so on, and so connecting with an allergist, endocrinologist for osteoporosis. Again, I don't think most dermatologists want to treat or feel

equipped to treat osteoporosis, but we can play a role in ensuring that they are connected with someone who will. Endocrinology, psychiatry. Depression, other psychiatric symptoms play a role in this very frequently. Having that connection and so on. In many respects, we can get the ball rolling on having patients see the correct specialties to ensure this multidisciplinary care.

Addressing SM Comorbidities: Recommended Therapies

The therapies are numerous because there are so many aspects, different kinds of symptoms, different organ systems involved. Some of them we heard earlier can be helpful in multiple respects, antihistamines and so on, but the consequences also need to be treated. Osteoporosis may require bisphosphonates.

Certainly, we have talked about epinephrine, the various treatments that Dr. Giannetti spent a lot of time on. It is important that these are getting put into action, but it also makes it difficult for patients because with a lot of treatments, there is polypharmacy, there may be different dosing schedules, regimens, different times.

This segues a little bit into part of the other aspect that I brought up earlier, which is the shared decision making, especially the idea of shared decision making, which is including patients in the process of identifying goals, treatment strategies, and so on, really transcends systemic mastocytosis. This is really a kind of approach that should be incorporated to all patient care. But there are some conditions where it plays a particularly important role, and something like this, where there is such a symptom burden, where there is a lot of treatment burden, it is important to elicit from patients what parts of their disease really impact them the most that they want to focus on. Maybe they do not have time to go to seven different doctor's visits in a week, which are the ones that they should be prioritizing, and then which ones can wait a little longer, and so on.

Shared Decision-making in SM

That is going to be different from person to person. That is really the idea here, seeking the patient's participation, helping empower them, educating them about their disease, and giving them some ability to buy into the treatment plan, when in an ideal world, that would not be necessary. We would wave our wand, and all aspects would be treated.

That is not the reality, so helping them to play a role in that really is crucial. Part of the consequence of that is that that patient buy-in is going to lead to better adherence and ultimately better outcomes because they feel like they are playing a role in their treatment.

Patient Support Resources

Here are some patient support resources. Very frequently, I am talking about educating patients, counseling them, connecting them. The reality is often clinics are very busy, and there may not even be enough time in one visit, one conversation to get all of that done. Providing patients with some resources to read at home to look into things can be helpful. Maybe they follow up, and there is the potential for a productive conversation that is not starting from scratch, but based on a lot of this background information that is put in terms that is accessible to the patients.

Posttest Question 3

We are going to return to the question from before. Margo has systemic mastocytosis, having some symptoms. Which of the following strategies would you recommend for Margo to prevent any life-threatening reactions caused by her indolent systemic mastocytosis?

A. Limit physical exertion to prevent future attacks.
B. Prescribe an antihistamine to use on-demand in case of an allergic reaction.
C. Carry an epinephrine autoinjector in case of future anaphylactic events.
D. Trial an elimination diet to reduce dietary triggers.

We will give everyone a few moments to answer. The vast majority of people identified epinephrine. Again, epinephrine is not the only treatment that is going to play a role here, by any means. Things like antihistamines, dietary triggers, and so on are important, but in terms of preventing a life-threatening reaction, that is really focusing on the anaphylaxis risk, and epinephrine autoinjector is key for that.

Key Takeaways

Some key takeaways. We have a few minutes for some questions as well. Please submit in the Q&A if you do have questions.

Some key takeaways. Refer patients for further assessment if systemic mastocytosis is suspected, ideally to a center that specializes in management of this condition. If not, nevertheless, further assessment is needed.

Treatment options for systemic mastocytosis include antimediator therapies and cytoreductive therapies. We heard different aspects about those.

Selective KIT inhibitors are important emerging and emerged treatment options. Because KIT mutations, particularly KIT D816V, are drivers of the pathophysiology, that targeted approach really is the way to address that.

People with systemic mastocytosis commonly receive many treatments and need adjustments. Communication with patients and HCPs is critical for optimal care again in that multidisciplinary setting.

# Question and Answer Session

We have a few moments for Q&A. I do see one here that I will get started with.

How early should patients with systemic mastocytosis be referred to assess bone health?

The short answer is immediately or within reason immediately. Patients are at high risk for bone disease, osteopenia, osteoporosis, fractures, and there is really no benefit to pushing that off. Either they are going to have more normal bone density and so on, and can be connected with an endocrinologist, let us say, for more preventative approaches, or they need to be treated as soon as possible. The short answer is essentially right away.

We will give a moment or two for additional questions. We do have another question. Maybe, Dr. Bitar, I will direct this to you. What can you do if a patient's GI symptoms improve but their skin lesions remain burdensome?

**Dr. Bitar:**
This is what I was talking about. We see that in autoimmune disease as well. Sometimes patients do get better in the other symptoms, and the skin will lag behind. As Dr. Giannetti mentioned, there are skin-targeted therapies. You can start with your antihistamine. I do use a lot of Xolair as well, as Dr. Giannetti mentioned, which is the omalizumab for skin. There is some talk about dupilumab, which is an interleukin-4 and 13 that also can control some of those pruritus, itching in patients. If you do want to have a kinase-targeted therapy, then they will be in the more advanced stage, as Dr. Giannetti mentioned. For the skin in particular, definitely all of them will be on antihistamine first and second generations in addition to omalizumab, and sometimes, considering as well, an interleukin-4 and 13 inhibitor. Definitely, now with the new BTK inhibitor for CSU, that is another consideration as well.

**Dr. Ungar:**
Thank you. Dr. Giannetti, I will pass the next one to you. How does avapritinib decrease the mutation?

**Dr. Giannetti:**
I assume this is asking about KIT D816V. Avapritinib has quite a bit of selectivity over wild-type KIT. As it turns out, the KIT D816V is a single point mutation that changes – I am using my hands here – changes what the kinase pocket looks like, and so avapritinib and the other tyrosine kinase inhibitors are designed to target that pocket. It specifically targets that pocket much more than wild-type KIT. It, for lack of a better word, turns off the KIT signaling, and so starves cells is how I describe it to my patients. You are selectively eliminating KIT D816V-bearing cells as opposed to wild-type KIT cells. When you measure the variant allele fraction, it is a simple measurement of KIT D816V reads over total reads. If your KIT D816V reads go down and your total reads stay the same, you have therefore decreased the mutational burden, mostly by the effect of killing off or eliminating the KIT D816V mutational-bearing mast cells.

**Dr. Ungar:**
Thank you. We have time for one more question. We have one more at the top of the list waiting. Dr. Giannetti, I will go back to you. Patient anticipates hepatic transplant. Can avapritinib be used at the same time?

**Dr. Giannetti:**
No, I would say. There is a risk of bleeding with these medications. Some intracranial bleeding. Bleeding more generally. It depends on what they are anticipating hepatic transplant for. I need a little bit more context here, but no, I hold avapritinib for about three to five days prior to surgery. I would say one possible exception, in aggressive mastocytosis, people often have hypersplenism, portal hypertension. In that case, which you have liver failure as a result of aggressive mastocytosis, the right answer may be to use avapritinib to cytoreduce, but that is a very specific case in which the primary cause of liver failure is systemic mastocytosis. In all other situations, the answer would be no.

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