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https://reachmd.com/programs/cme/indolent-systemic-mastocytosis-ism-treatment-options-for-ism/13995/

Released: 09/30/2022
Valid until: 10/07/2023
Time needed to complete: 15 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Indolent Systemic Mastocytosis (ISM): Treatment Options for ISM

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Welcome to CME on ReachMD. This activity, entitled “Indolent Systemic Mastocytosis (ISM): Treatment Options for ISM” is provided by Prova Education.

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Dr. Radia:

Indolent systemic mastocytosis, ISM, is the most common form of systemic mastocytosis, which results from excessive accumulation of mast cells in various tissues, leading to chronic and episodic mast cell mediator release. Are you up to date on the current and emerging treatments for ISM?

This is CME on ReachMD, and I'm Dr. Deepti Radia.

Dr. Akin:
And I'm Dr. Cem Akin.

Dr. Radia:
So early diagnosis is one of the keys to successfully treating ISM. Let's briefly review the importance of creating awareness about ISM amongst all healthcare professionals. Cem, what are the indicators that a patient may have ISM that all healthcare providers should look for?

Dr. Akin:
ISM is a rare disease, so it is often overlooked in the general healthcare setting, and these patients may present with a variety of different organ system symptoms. The most common manifestations are related to skin, gastrointestinal [GI] tract, and neurocognitive domains.

Many of these patients have these skin spots called urticaria pigmentosa or maculopapular cutaneous mastocytosis.

The other skin-related symptoms include flushing as well as itching. Gastrointestinal-wise, we see a lot of abdominal cramping. Patients presenting with diarrhea sometimes alternating with constipation. Neurocognitive symptoms like brain fog, fatigue, and memory problems are also very common, along with musculoskeletal pain that may resemble fibromyalgia.

Dr. Radia:
Cem, the skin and anaphylaxis is quite important and the GI symptoms. When a primary care physician sees a patient with maybe that constellation, which specialist do you think they need to refer to?

Dr. Akin:
I think 2 important specialists in this regard are allergists and hematologists. Hematologists really make the diagnosis of indolent systemic mastocytosis because it requires a bone marrow biopsy and aspirate to look for certain criteria. And allergists can help

manage mast cell-mediated related symptoms.

Dr. Radia:
All right. And I'm just also thinking do all patients with ISM have significant rash or spots?

Dr. Akin:
No. The majority of them do, about, I would say, 80% would have the spots. But another 20% may present without any skin findings. And in those patients, it's important to have a high index of suspicion, especially if they're presenting with recurrent hypotensive anaphylaxis which may or may not be associated with flushing and abdominal symptoms.

Dr. Radia:
Cem, I want you to imagine you're seeing a 33-year-old female patient who was referred to you by her primary care physician, suspecting that she has some sort of mast cell disorder. The patient's main complaint is that she has frequent symptoms of itching, flushing, stomach pain, and often feels fatigued. Her CMP [comprehensive metabolic panel] and CBC [complete blood count] results come back as normal. What other approaches would you use to diagnose this patient with ISM?

Dr. Akin:
I would start with a very comprehensive skin examination to make sure that the patient does have the skin spots of urticaria pigmentosa. So if you detect urticaria pigmentosa spots, the chances of this patient having systemic mastocytosis is greater than 95%. And I would refer this patient to a hematologist for a concrete diagnosis.

If the patient does not have skin symptoms, so I would start with a baseline serum tryptase level. It is very important to substantiate this diagnosis with histopathology and the findings in the bone marrow biopsy.

Now you may also want to screen the peripheral blood for KIT D816V mutation. So this is a mutation that occurs in the mast cell progenitor and it results in clonal expansion of the mast cell, and it's seen in more than 90% of patients with indolent systemic mastocytosis. That mutation is also examined in the bone marrow biopsy and the bone marrow aspirate.

So once the decision is made to go forward with the bone marrow biopsy, then the bone marrow should be examined for mast cell collections with tryptase staining. And those mast cells express aberrant markers—CD2, CD25, and CD30—which could be detected by immunohistochemistry or by flow cytometry. And of course, the mutation that I mentioned, KIT D816V, should also be detected in the bone marrow aspirate after the procedure.

Dr. Radia:
When my colleagues, dermatology colleagues, refer patients to me, the clinical examination is really quite important because these patients don't have any organomegaly. They don't have an enlarged liver or spleen. So that also helps with making that diagnosis.

Dr. Akin:
I think patients with indolent disease, they do not necessarily manifest as a hematology patient with splenomegaly or hepatomegaly or even blood count abnormalities. So I think a skin examination is crucial, with the high index of suspicion. Especially in people with recurrent hypotensive episodes, a bone marrow biopsy is required.

Dr. Radia:
This female patient that you've seen has the confirmed diagnosis. Looking at the current treatment, and based on her symptoms and trigger avoidance, what would you say are the most common triggers that you've seen in patients with ISM? And how would you educate this patient on these triggers?

Dr. Akin:
That's a very important aspect of management of indolent systemic mastocytosis, because these mast cells can and will be triggered by different stimuli. The most common ones are exposure to heat, humidity, or to cold temperature changes. Friction. Acute emotional stress, especially for flushing, and skin symptoms, as well as abdominal symptoms. Very strenuous exercise. Sometimes we see that as a trigger. Alcohol and spicy foods can also nonspecifically degranulate the mast cells. Infections are a common trigger because mast cells have receptors for markers of inflammation, like complement or even the products that are released from bacterial or viral surfaces. And certain medications that could be used in anesthesia perioperatively that may include certain muscle relaxants, NSAIDs, and opioids or radiocontrast agents can trigger mass cell release in a small number of patients.

Finally, bee or wasp venoms can trigger very severe anaphylaxis in some patients. The likelihood of mastocytosis is about tenfold higher than general population in somebody who presents with very severe venom anaphylaxis.

Dr. Radia:

So assuming that you've just talked to this particular patient about trigger avoidance, if she needed to have treatment or anti-mediator therapy or treatment for her ISM, what sort of treatments would you be considering?

Dr. Akin:
I think first of all, my approach is to prescribe a self-injectable epinephrine to all of my patients with indolent mastocytosis, because the lifetime prevalence of anaphylaxis can be up to 50%, and sometimes there are really no predictive markers who will go into anaphylaxis versus not. And some episodes may be completely idiopathic without any obvious IgE [immunoglobulin E]-mediated triggers.

Beyond that, we use prophylactic therapies directed at mast cell mediators. And the mainstay of treatment is antihistamines, especially H1 antihistamines. We try to stick with non-sedating second-generation H1 antihistamines. These could be supplemented with an H2 antihistamine like famotidine for people with abdominal symptoms. Another drug that's useful for patients with abdominal symptoms is cromolyn, oral cromolyn sodium that can be taken up to 4 times a day before meals. Sometimes we'll use antileukotriene agents such as montelukast.

The other options include omalizumab, which is an anti-IgE monoclonal antibody. It is not an FDA-approved indication to use this drug in mastocytosis, but if somebody is having continued recurrent hypotensive or mast cell activation episodes, despite being on a good combination of anti-mediator drugs, omalizumab can be considered as an off-label treatment.

And finally, if an indolent systemic mastocytosis patient is still having a lot of disabling symptoms, especially anaphylactic, despite being on a number of these medications, cytoreductive agents or a referral to a clinical trial that employs mast cell cytoreduction could be considered, especially with one of the new tyrosine kinase inhibitors that directly target D816V KIT mutation.

Dr Radia:
For those of you tuning in, you're listening to CME on ReachMD. I'm Dr. Deepti Radia, and here with me today is Dr. Cem Akin. We're discussing the most up-to-date strategies for diagnosing and treating ISM.

There are several investigational ISM drugs undergoing clinical trials right now. Can you discuss some of the emerging data from these trials in ISM, please?

Dr. Akin:
The drug that is farthest advanced in a clinical trial in terms of a specific D816V KIT inhibitor is avapritinib. There's a trial called PIONEER. It is currently closed for enrollment, but the company just announced topline data from over 250 patients. And these patients were divided into placebo versus 25 mg of avapritinib. After 24 weeks of treatment, there were significant reductions in symptom scores across all domains. And these reductions continued to improve by week 48. The drug was safe and tolerable. Less than 1% of the patients in the active drug discontinued the medication due to adverse event. And the serious adverse events were 5% in the treatment arm versus 11% in placebo. So it emerges as an interesting, exciting clinical option for patients who do not show optimum response to anti-mediator treatments.

There are other D816V-specific inhibitors, including BLU-263 and bezuclastinib, that are currently in clinical trials. Those trials are open to new patient enrollments. There is no publicly available data from those trials at this point.

There is a drug called masitinib that is in a phase 2 clinical trial. That drug is different in that it does not have a D816V KIT inhibitory activity, but inhibits the wild-type KIT, so it is not expected to cause significant cytoreduction. But in an earlier phase 2 clinical trial, it has been shown to cause some modest symptom reductions in patients, probably due to the inhibition of Src and Lyn kinases, which are involved in mast cell activation.

There is a drug called midostaurin that has been approved for treatment of advanced disease that has also been tried in indolent disease in a small open-label clinical trial. And it did show improvement in symptom scores, except for nausea and vomiting, which is a common side effect of the medication. But none of these drugs are approved for treatment of indolent systemic mastocytosis, and we will await for further data and FDA evaluation to see if we can use some of them in our future treatments.

Dr. Radia:
How do you think these emerging agents will impact on the patient and clinicians with patients with ISM?

Dr. Akin:
First of all, if these drugs really work as has been shown in the clinical trials, they will reduce the polypharmacy requirement of the patients. And they also seem to be very effective in reducing skin spots and skin lesions, which in addition to being symptomatically bothersome, also can present a cosmetic challenge to the patient. So I think those are some of the advantages that these drugs would bring to patients if they are not getting enough symptom relief with the first-line anti-mediator treatment options.

Dr. Radia:
So it's been a fascinating conversation, Cem, as usual. And before we wrap up, do you have one take-home message for our audience?

Dr. Akin:
I would say consider a serum tryptase level in a patient presenting with recurrent unexplained anaphylaxis or bee venom anaphylaxis is my one take-home message. And if those patients have elevated tryptase level, please consider for referral to a hematologist or an allergist.

Dr. Radia:
Perfect. And I guess mine as a hematologist is that there's always hope. So these patients that have been on polypharmacy and multiple anti-mediator therapies, may now, with the new targeted drugs, have a way of having a significant improvement in their quality of life, which is excellent. So think about the trials that are available for your patients to see if they're eligible.

So unfortunately, that's all we have time for today. I want to thank our audience for listening in and thank you, Cem, for joining me and sharing all of your valuable insights. It was great speaking to you today.

Dr. Akin:
Thank you very much, Deepti, for having me. I really enjoyed the conversation.

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