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What Are the Recent Updates to Guideline-Driven Care in Non-Advanced Systemic Mastocytosis?

Announcer:
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Dr. Akin:
Hello, my name is Cem Akin. I'm a Professor of Medicine at the University of Michigan, and I will talk about the Recent Updates to Guideline-driven Care in Non-Advanced Systemic Mastocytosis.

Before talking about the care of patients with systemic mastocytosis, I would like to mention that the classification and diagnostic criteria of systemic mastocytosis were just updated last year. And this update came in the form of two different groups. And fortunately for us, they overlap to a great extent in between these recommendations. The first group is the World Health Organization Group. And this was published in *Leukemia*. And the second group is International Consensus Classification, or the ICC group, and that was published in the journal, *Blood*.

For the most part, these diagnostic criteria and classification remain similar to the previous versions, but there were some changes that I highlighted in yellow font here in the slide. So this is the diagnostic criteria. And as you see, they consist of one major and four minor criteria. And in order to be diagnosed with systemic mastocytosis, the patient needs to have either one major plus one of these four minor criteria, or in the absence of major criterion, three minor criteria. So what are these?

The major criterion is characteristic multifocal dense infiltrates, each consisting of 15 or more mast cells per aggregate in the bone marrow or another extracutaneous tissue. And these mast cell infiltrates are best visualized by tryptase or CD117 immunohistochemistry.

And the minor criteria, the first one is the morphology of the mast cells being spindle shaped in bone marrow aspirate smears. And this criterion specifically applies to the bone marrow because you can see spindle-shaped mast cells in other tissues like skin or even gastrointestinal tract. So it is good to keep that in mind. The second criterion is detection of a codon 816 KIT or another activating mutation. So the other activating mutations were just added in the 2022 version of these criteria that were proven to cause a ligand independent activation of the KIT molecule. And the important aspect of this criterion is that when detecting for the kid mutations, a high sensitivity method should be used. And these are generally allele specific or digital droplet PCRs, which are capable of detecting less than 0.1% of allele burden. For example, methods such as next gen sequencing or sequencing-based methods usually do not have the high sensitivity needed to detect this mutation, especially in some patients with lower mast cell burden, because we are here trying to detect a somatic mutation, that is not a germline mutation. So it will be only present in the minority of the cells and you need to have a high sensitivity test to be able to detect that. The third minor criterion is expression of CD2, CD25, and as added in 2022, CD30 by the bone marrow mast cell population. And this expression can be detected by either immunohistochemistry or flow cytometry. And CD30 is especially a valuable marker for the well-differentiated form of systemic mastocytosis, because these patients, they constitute the

minority fraction of the overall patient population, but they do not express CD2 and 25. And sometimes they don't even have the codon 816 mutation. So it is important to keep in mind that CD30 can come in as a useful marker in these cases. And then the final criterion is serum tryptase level greater than 20 nanograms per milliliter. And just as a reference, the median serum tryptase level is around 5 nanograms per milliliter, and it is a marker of surrogate marker of mast cell burden. And this criterion is not valid if there is another associated myeloid disorder, such as myeloproliferative or myelodysplastic syndrome, because myeloblasts also contains small amounts of tryptase, and the serum tryptase in these patients may be elevated regardless of mastocytosis.

And this is a slide showing what I just talked about. On the left upper corner, you see the major criterion with the compact mast cell infiltrates stained in a bone marrow biopsy section with tryptase. And on the top right corner, you see these spindle-shaped hypogranulated atypical mast cells. And in the lower panel, you see the flow cytometric detection of CD25 positive cells on the x-axis plotted against the CD117 KIT which is expressed on all mast cells on the y-axis. And on the left, you'll see a normal population without CD25. And on the right, you see a patient with mastocytosis who has expression of CD25. And as I mentioned, this can be also done is an immunohistochemical staining with CD25.

The classification of mastocytosis is shown here. We can broadly categorize systemic mastocytosis into non-advanced and advanced forms. And the non-advanced forms are indolent systemic mastocytosis, which make up the majority of the patients. And new in 2022, there is a new category called bone marrow mastocytosis. So these are patients with no skin lesions, and generally lower mast cell burden with the tryptase levels less than 125. And then on the other end of the spectrum is the higher mast cell burden with smoldering systemic mastocytosis, which require two or more B-findings, as you see in the slide, that indicate higher mast cell burden. New in 2022 KIT D816V variant allele fraction or allele burden of greater than 10% was also added as a new B-finding. And on the lower part of the slide, you'll see the advanced mastocytosis, and these present with a variety of aggressive features such as C-findings, indicating organ damage due to mast cell infiltration, or presence of other hematologic disorders or mast cell leukemia.

Now, how do we manage patients with non-advanced systemic mastocytosis? Now, it is important to make the point that these patients generally have a comparable life expectancy to general population. But that doesn't mean that they are not suffering from this disease. They can experience a variety of mast cell activation symptoms due to triggers. And these triggers vary depending on the patient. And they can include things like temperature changes, friction, stress, alcohol, exercise, certain medications, like nonsteroidal anti-inflammatory drugs or opioids, and Hymenoptera, things like honeybees or Vespidae stings.

There is a need to screen these patients for osteoporosis because about 1 out of 3 patients with non-advanced systemic mastocytosis may have osteoporosis and may suffer compression fractures, especially of the spine. And the mainstay of the treatment is prophylactic pharmacotherapy for mast cell activation symptoms. And depending on the symptom level, this may range from only as-needed treatment, often H1 antihistamine for example, to daily scheduled multiple classes of anti-mast cell mediator therapies like H1 and H2 antihistamines, leukotriene blockers, and so on. And then of course, management of associated comorbidities like osteoporosis, or Hymenoptera venom allergy is an important part of the overall strategy of patient treatment.

Now, if we look at the stepwise pharmacological management of non-advanced mastocytosis, we always start with a nonsedating long-acting HI antihistamine, such as cetirizine, fexofenadine, or loratadine. And these can be administered once or twice daily, and could be supplemented with a shorter-acting antihistamine, such as diphenhydramine or hydroxyzine, if needed. And if this is not sufficient to take care of the symptoms, depending on what the symptoms are, one might add a leukotriene blockers such as Montelukast and an H2 antihistamine such as famotidine which also works for abdominal symptoms and phototherapy. And for abdominal symptoms, as I mentioned, H2 antihistamines, proton pump inhibitors, cromolyn sodium, and leukotriene blockers. And for recurrent hypotensive anaphylactic episodes which may occur in some patients, we usually use leukotriene blockers in addition to H1 antihistamines and H2 antihistamines. For a recurrent anaphylaxis refractory to these treatments, we usually consider adding omalizumab, which is an anti-IgE monoclonal antibody. And this is of course used as an off-label treatment in these patients. And occasionally glucocorticoids may be used for short terms in patients with anaphylactic episodes, or some patients with refractory diarrhea.

And if there is no response to any of these groups of treatments, then these patients would be candidates for clinical trials targeting either mediator-related symptoms, or a targeting the mast cell cytoreduction itself.

I hope this review was useful in considering the general classification, diagnosis, and management principles guiding non-advanced systemic mastocytosis. Thank you for your attention.

Announcer:
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