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

Current Guidelines and Management of Non-Advanced Systemic Mastocytosis

Announcer:
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Dr. Giannetti:
Hi, everybody. Thank you for being here. My name is Dr. Matt Gianetti. I'm one of the assistant professors at Harvard Medical School and Brigham and Women's Hospital and the associate director of the Mastocytosis Center there. I'm here to talk to you a bit about current guidelines and management of the non-advanced variants of systemic mastocytosis, particularly indolent systemic mastocytosis and smoldering systemic mastocytosis. This will be the first of a couple of presentations regarding different topics of treatment and monitoring of mastocytosis.

Okay, so I'd kind of like to start off with this slide because it's conceptually easy to identify how I at least think about treatment of mastocytosis. So you see here a picture of a mast cell and it makes a bunch of things, either preformed mediators, lipid mediators, chemokines, cytokines. The specific things it secretes are less important than that it secretes things that can cause a lot of symptoms. So, based on that notion, part one here, antimediator therapy, will be basically blocking the things that mast cells secrete or release that cause symptoms.

That would be one conceptual form of therapy. The second conceptual form of therapy is directly reducing the mast cell burden. So in systemic mastocytosis you have a multiplication of mast cells and you have more mast cells infiltrating various organs. Simply by the mass of the mast cells you can have symptoms and thereby the second strategy is directly eliminating or killing these mast cells. So two primary strategies to think about: treatment of the mediators and directly cytoreducing mass cells. We'll talk a little bit about the first point here, the antimediator therapy. There will be more coming on how to directly reduce mast cell burden. On that note, the National Comprehensive Cancer Network Guidelines released a series of recommendations for systemic mastocytosis. I think this is a pretty good conceptual framework.

Certainly, there are a little bit of management points that I would do a bit differently and I think it's really helpful in these rare diseases to send patients to centers of excellence, so a specific center where they have lots of experience with antimediator therapy, cytoreductive therapy, et cetera. But as a general guide this is an excellent guide for general management. They have a couple primary tenets of management: one, commonsense avoidance of triggers. Two is a step-wise treatment approach to prevent mediator release symptoms.

We'll talk about a couple of the medications in the coming slides about how to escalate that step up. Acute treatment of anaphylaxis, particularly giving these patients an epinephrine autoinjector. And then finally cytoreductive therapy to reduce the mast cell burden. So on the specific therapies I want to talk about classification of antimediator therapy. So these are all things that do not reduce the amount of mast cells but instead block mast cell activation or block components, bioactive mediators released by mast cells. We have H1-antihistamines, H-2 antihistamines, mast cell stabilizers, so cromolyn or ketotifen. And then we have biologics such as omalizumab.

In the other category, intramuscular epinephrine, it is technically antimediator therapy but this is really reserved for acute settings during

the anaphylaxis and then systemic steroids, these are often used as adjunctive therapies, particularly during the flares or a particularly severe bout of symptoms. So one of the main things about mastocytosis is that in this disease mast cells dramatically overproduce mediators. So there's a couple of canonical mediators that mast cells produce but I have highlighted two pieces of literature here showing an increase in methylhistamine in systemic mastocytosis over a group of healthy control patients and leukotriene E4 you can clearly see here is overproduced in mastocytosis compared to a control group.

Both of these are two of the primary mediators of mast cells and clear focuses of antimediator therapy. Histamine in particular is the major bioactive mediator that we like to focus upon. So H1-antihistamines, these are oral, over-the-counter in most part medications that are regularly prescribed for seasonal allergic rhinitis, that chronic urticaria. And because one of the hallmarks of mastocytosis and shown on the previous slide is overproduction of mediators, particularly histamine, we rely heavily on H1-antihistamines.
We're not going to go over all of them here, but I want to draw a major distinction between first generation and second generation antihistamines. First generation are the older medications. So think of chlorpheniramine, Benadryl, Periactin, older medications like this that freely cross into the blood-brain barrier and have sedating side effects. They also have a considerable amount of anticholinergic side effects. This is in stark contrast to the newer generation, called the second generation antihistamines. These molecules were designed to have limited penetration of the blood-brain barrier, and as a result they're much less sedating. Several examples in this class would include cetirizine, fexofenadine, loratadine, et cetera.

My strong preference is to start with second-generation oral antihistamines. H2-antihistamines, primarily famotidine, ranitidine which is no longer on the market, and cimetidine, which is an older medication. These are sold also over the counter primarily as antacids, but interestingly they worked directly as histamine antagonists. So you can see here in this picture histamine directly stimulates parietal cells in the stomach to produce acid. And so blocking histamine at the H2 receptor decreases the parietal cells' ability to stimulate acid. So this directly combats gastrointestinal symptoms which are quite common in mastocytosis. We term it hypersecretion.

A couple of other medications here, so oral cromolyn has some literature to improve gastrointestinal symptoms in systemic mastocytosis. You can see here at the bottom, this is a nice crossover study done here at the Brigham many, many years ago where patients have baseline symptoms here on cromolyn and then they crossover to cromolyn or placebo. And as you can see here the symptom scores are quite a bit higher on placebo versus cromolyn. And important to recognize this is gastrointestinal symptoms scores here, so cromolyn is very poorly absorbed into the bloodstream and it works quite well for gastrointestinal symptoms but does not work for non-gastrointestinal symptoms. So that's important to keep in mind.

Omalizumab, this is a monoclonal antibody directed at IgE. This is more commonly in the hands of the allergist/immunologist but can be used and prescribed by anybody who is comfortable. This is a small case series from a group out of Denmark and Odense Hospital where they show quality-of-life score and then fragment it into multiple different domains and look at how patients do at baseline and then compared to on omalizumab.

So small case study involving just 14 patients but you can see here, in terms of overall comprehensive quality-of-life score, basically everybody has had a decrease or an improvement in quality of life. Fragmented out in individual domains, by far omalizumab is the most helpful for anaphylaxis and cutaneous manifestations, and this actually makes sense. There's a robust series of data showing reductions of IgE-mediated anaphylaxis, and, in fact, omalizumab carries FDA approval for chronic spontaneous urticaria which is a disease of the skin. Last, but certainly not least, anaphylaxis is very common in systemic mastocytosis.

You can see here on the left, about 50% of adults who have systemic mastocytosis report an episode of anaphylaxis at some point in their life. Looking a little bit in more detail, adults who have either cutaneous or systemic mastocytosis, it is much more prominent in those with systemic mastocytosis. In terms of triggers on the right hymenoptera stings. So hymenoptera is a class of stinging insects that contain venom. Classically, we think of honeybee, wasp, yellow jacket, white hornet, and yellow hornet as the primary drivers of this.

Fire ant can also cause anaphylaxis although not as included in the order hymenoptera. So hymenoptera is the most common trigger of anaphylaxis in those with mast cell disorders. We see second, third, and probably fourth are food, drugs, and then idiopathic. Because the incidence of anaphylaxis is so high in this patient population, we recommend all patients be prescribed an epinephrine autoinjector and this can be prescribed by any provider, whether it's dermatology, oncology, allergy, primary care medicine. It's a very important tenet in the treatment of mastocytosis. So that's all for this part. Thank you very much for your attendance and look forward to seeing you in the next section. Thank you.

Announcer:
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