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Targeted Therapy for Non-Advanced Systemic Mastocytosis

Announcer:
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Dr. Giannetti:
Hello, everybody. Thank you for attending today. My name is Dr. Matthew Giannetti. I am an allergy immunology provider at the Brigham and Women's Hospital in Boston, Massachusetts. Also a Assistant Professor of Medicine at Harvard Medical School and the Associate Director of the Mastocytosis Center here at the Brigham. I'm here to talk to you a bit today about targeted therapy for non-advanced variants of systemic mastocytosis. This is part of a series, so I really encourage all of you to look at the other parts within this Non-Advanced Variants of Systemic Mastocytosis Series. So again, I showed this therapy at the last one.

I'm not going to belabor this point here, but I think conceptually, it's really important to think of treatment of mastocytosis as two different highways, if you will. Highway one is anti-mediator therapy, so blocking the things that mast cells secrete and release. And highway two is directly reducing the mast cell burden with cytoreductive therapy. The anti-mediator therapy is important in all forms of mastocytosis, whether it's advanced or not. And reducing the mast cell burden, classically, has been most important for the advanced variants of systemic mastocytosis. But as you'll find out in the coming minutes here, we've really shifted this towards thinking about this in symptomatic patients with non-advanced variants of mastocytosis. The hallmark of targeted therapy is targeting the KIT mutation. So it's really important to understand that activating mutations in the KIT protein defines systemic mastocytosis. So basically, all patients who have systemic mastocytosis have mutations in the KIT protein.

This here, on the right, is an older picture from the French group, showing a variety of mutations both in children and adults. The takeaway point here is that really, you can have mutations at any point throughout the KIT protein but there is a genotype/phenotype correlation. And so what that means is different mutations may portend different clinical prognoses, clinical symptoms, et cetera. What I would like to draw attention to, at first here, is this D816V mutation. So this is the highlight mutation in the vast majority of patients with systemic mastocytosis.

Depending on the literature, it's 90, 95% or so of patients, and it's found here in the activation loop. This causes the KIT protein to be constituently active and drives much of the symptoms associated with systemic mastocytosis. So on the words here, you can see the highlight, the most common mutation, by far, is D816V. So as I mentioned before, KIT D816V is prevalent in systemic mastocytosis and it is generally the defining mutation of systemic mastocytosis.

The vast majority of patients with indolent systemic mastocytosis, and in fact, other variants of systemic mastocytosis will have detectable KIT D816V mutation or other activating mutations. This is critically important because it's a targetable mutation. So it forms the foundation of conceptual treatment with targeted tyrosine kinase inhibitor therapy, which we'll talk about in the next couple slides. So this here is a nice study that was done, maybe about 10, 12 years ago, in which the authors fragmented, flow cytometricaally, different parts of the differential and looked for the presence of D816V mutation in different cell lines. You can see here in 100% of the mast

cells, it was detected. I think this is maybe not repeatable, it's probably lower than 100%. But it argues the case that in the vast majority of patients, D816V is in fact detectable in the mast cell lineage. Super important point here. So KIT D816V testing must be tested via a PCR-based method.

So, this has become standard of practice at present. Although Quest and some other, you know, private laboratories do offer next generation sequencing it's really important that it's a PCR-based test. So this is just a little graphical depiction of how PCR works. I imagine the vast majority of listeners will understand this. But I think conceptually understanding how it works is important to understand why we want you to do PCR rather than me just telling you to use PCR. So what we do here, is we have primers that are targeted towards a D816V mutation. And if, for example, somebody has one single cell that has a D816V mutation, we will run it through a series of amplification, which will amplify that D816V mutation over and over and over and over again. And then when we go back to look at it, there will be a bunch of it. It will be very easily detectable because we have, in fact, amplified it. This is in contrast to next generation sequencing, despite the name is not really next generation, where you're directly looking for the mutation.

So, the sensitivity here, next generation, about 1%, this is really even generous. I would probably say two to 3%. Whereas digital droplet PCR can go down, almost to .01%. And you can see very nicely here, the dots are which KIT D816V was detected. So above 1%, you can use, probably both methods to detect it, but anything below that, which is the majority of patients, at least in our cohort here at the Brigham, you will have a negative test if checked via next generation sequencing. But in fact, positive to digital droplet PCR. D816V is very important to identify and you want to make sure that the data is accurate. So using a PCR-based method really is important in this situation.

Okay, targeted tyrosine kinase inhibitors. So as we mentioned before, these therapies are targeted towards D816V mutation and other activating mutations in KIT. So the concept behind them is that they are directly cytotoxic. So we're targeting a mutation that is crucial for survival of mutated mast cells. By blocking that mutation, you will lead to cell death of the mast cells. We have two currently approved tyrosine kinase inhibitors, Avapritinib for advanced systemic systemic mastocytosis and also Midostaurin for advanced systemic mastocytosis. There are several molecules under investigation. Avapritinib is under investigation for ISM, as is BLU-263. And then finally Bezuclastinib is under investigation for both indolent and advanced variants of mastocytosis. So I wanna talk a little bit about the specific molecules and share some data.

So, this here is Midostaurin. This is from really a hallmark paper, which was published in New England Journal in 2016, the lead author with Jason Gotlib from Stanford. So Midostaurin is a multikinase inhibitor. It's not technically a targeted kinase inhibitor. It was approved for advanced systemic mastocytosis in April, 2017. Because it's a multikinase inhibitor, it does hit other tyrosine kinases as well, particularly the FLT3 protein. And FLT3 is a known mutation that's that can be seen in AML. Midostaurin also carries approval for FLT3 positive AML.

There's limited data for ISM, although there are a couple of studies showing it improve quality of life and some symptom scores. And you can see here, in these markers, in best percentage change from baseline, significant and rather dramatic reduction in mast cell burden. Similar changes to serum tryptase levels and similar changes to spleen volume. The hepatosplenomegaly is something that's really reserved for the more advanced variants in smoldering systemic mastocytosis. We see this less frequently in indolent systemic mastocytosis. But the bone marrow changes and the serum tryptase changes are impressive and are what led to approval of this medication.

Moving forward a bit to talk about Avapritinib. The pioneer study is a phase two study that was designed to evaluate efficacy and safety of Avapritinib versus placebo in indolent systemic mastocytosis. Patients were randomized to Avapritinib versus placebo, and then primary endpoints were drawn at 24 weeks. And the primary outcome was reduction in change of TSS, or a symptom score based on itching, gastrointestinal symptoms, other symptoms seen with mastocytosis. They also looked for key secondary endpoints, so things that were not purely symptom scores, but were more biochemical or laboratory markers.

So, reduction of tryptase, reduction of D816V allele fraction and bone marrow mast cells. So looking at this data, you can see that at 25 milligrams daily, Avapritinib does have significant benefits over placebo. So in this here, ISM-SAF, this is the symptom score questionnaire that we used at 24 weeks. You can see, in placebo, no significant response rate, but 60% of patients on Avapritinib had an improvement. So this met primary endpoint. And then the key secondary endpoint was reduction of serum tryptase, greater than 50% at 24 weeks. And again, this met secondary, the criteria 70% had reduction in serum tryptase by greater than 50%.

So this really is the first drug that's been studied exclusively in indolent systemic mastocytosis. So it's really quite a novel therapy. There are others coming, that are currently under investigation as well. The monitoring and management of tyrosine kinase-related adverse effects. I would say that treatment with the targeted tyrosine kinase inhibitors right now is really in the infancy. Most of these, all of these medications, at least for the non-advanced forms are exclusively via clinical trials. We'll talk about some of the common adverse effects. As you know, we are hopeful in the future, some of these will be approved.

So, first things to note, the common adverse effects. Really, all of these are dose-dependent and it's important to draw distinction between doses used for the more advanced variants of systemic mastocytosis and the doses used for indolent systemic mastocytosis. So most common adverse effects, we see myelosuppression, nausea, vomiting, diarrhea, and edema. I would say probably, the edema and gastrointestinal side effects tend to be the most disturbing to patients. At lower doses, for indolent systemic mastocytosis, usually they are more of a nuisance and the overall benefits outweigh therapy. But some patients can have difficulty tolerating them. I would also add to this list, cognitive changes.

We do have some memory issues, forgetfulness, cognitive slowing, things that have come up as reproducible side effects for the targeted tyrosine kinase inhibitors. Midostaurin also has a interstitial lung disease or pneumonitis as a known rare but quite serious side effect. And then Avapritinib, thrombocytopenia. We do recommend discontinuation of the medication at low platelet counts. This is primarily due to the incidence of intracranial hemorrhage that were noted in the more advanced populations. There have been several instances of severe intracranial hemorrhage in these patients. So overall, tyrosine kinase inhibitor therapy in indolent and smoldering systemic mastocytosis. This is really a game-changing approach. It looks very promising.

But again, as I mentioned before, we're still in the infancy of these medications. We need a lot more clinical trial data. And then after they're FDA approved, I think providers need more routine experience with these medications. First line therapy, in basically all situations, is anti-mediator therapy. In the more advanced variants, they require cytoreductive therapy. But in general, anti-mediator therapy is useful for all variants of systemic mastocytosis. And then most importantly, for anybody who is not well-controlled please refer to a center of excellence for consideration of a clinical trial. I've spent lots of time talking about these fancy new medications. But again, as of the time of this presentation none of them are FDA approved for indolent or smoldering systemic mastocytosis. So referral to a center of excellence is needed to enroll these patients in clinical trials. Thank you very much for your time and attendance, and I look forward to seeing you in our next session. Thank you.

Announcer:
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