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

Rationale for Tyrosine Kinase Inhibitors 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 would like to talk about the rationale for tyrosine kinase inhibition and non-advanced systemic mastocytosis in this episode.

Non-advanced mastocytosis is the most common form of mastocytosis, and is generally associated with a normal or a near-normal life expectancy. But these patients do suffer from a variety of different mast cell activation-related symptoms. As you see in the slide, the impact on quality of life in patients with mast cell disorders can be very significant. Unpredictability of the symptoms ranked as the number one concern in this survey that we conducted back in 2014. But various other aspects like inability to work, fatigue, gastrointestinal complaints, and anaphylactic episodes, and fear and anxiety of dealing with an unknown or a rare disease also, were cited frequently.

The symptom burden and systemic mastocytosis can be measured in different ways. This is one way of measuring it, it's called Symptom Assessment Form is developed by Blueprint Medicines. And it asks for 11 different domains: bone pain, abdominal pain, nausea, and so on, as you see in the slide. And each of these symptoms are scored from 0 to 10. So in a patient with very severe symptoms, the maximum score one can get is 110. And in patients with no symptoms, the minimum score is 7.

These patients also experience work impairment as a result of having this disease. For example, reduced – they may have to reduce their work hours, they might quit their jobs, or take an early retirement, about 1 out of 3 patients go on medical disability, and even terminated from the job. And they do get injectable epinephrine, because the risk of anaphylaxis is approximately 50% in adult patients through the lifetime, and some of these patients use the epinephrine as needed for these anaphylactic symptoms. And when you compare the symptom burden and systemic mastocytosis to other diagnoses, we see that this is looking at SF 12 symptom scores, it is actually very comparable to other disorders that you see here, like colorectal cancer, anemia, depression, and so on.

So this is why we keep looking for new treatment options. The standard treatment in mastocytosis is anti-mediator treatment, including H1 and H2 antihistamines and leukotriene blockers, and a variety of other anti-mediator targeting drugs. But when this is not enough, and the patient is experiencing these disabling symptoms, then we consider the next step, which is the cytoreductive treatment in non-advanced mastocytosis. Now, the cytoreductive treatments have already been used as an approved form of treatment in advanced mastocytosis. And as I mentioned, they are also being employed in indolent systemic mastocytosis refractory to symptomatic treatments. And traditionally, these agents consisted of alpha interferon and cladribine before the emergence of tyrosine kinase inhibitors, because the new kinase inhibitors now have not only more efficacy, but also lower toxicity than alpha interferon and cladribine.

Tyrosine kinase inhibitors work by inhibiting the disease driving mutation, D816V KIT in mastocytosis, and they can be separated into three broad categories: wild-type KIT inhibitors, and the prototype here is imatinib. And this drug is unfortunately not a viable option for

the majority of patients, because the majority of the patients have the D816V KIT variant. And then midostaurin is the prototype that has been FDA approved for advanced systemic mastocytosis and it inhibits both wild-type and D816V. Dasatinib does have some activity in vitro, but is not a very good in vivo medication for these patients. And then primarily D816V KIT inhibitors, and in this group we have avapritinib, which is FDA approved for advanced mastocytosis. And also elenestinib and bezuclastinib.

Avapritinib has been evaluated in non-advanced systemic mastocytosis in PIONEER trial, and this trial compared 25 mg of avapritinib to placebo over a course of 24 weeks. And the primary endpoint was reduction in symptom scores as assessed by Symptom Assessment Form that I mentioned earlier. And as you see here, the red line here indicates the placebo, and the blue line is avapritinib. And there is a significant difference in symptom reduction between placebo and 25 mg of avapritinib. And when the placebo patients rolled over to 25 mg of avapritinib in the open part of the trial, all of those patients eventually caught up with the avapritinib extent of symptom improvement. This trial also resulted in reduction of mast cell burden and surrogate marker of mast cell burden such as tryptase levels, bone marrow mast cell infiltrates, and the burden of D816V allele in peripheral blood and bone marrow.

The next slide is about the investigational KIT targeting – D816V targeting tyrosine kinase inhibitors, elenestinib and bezuclastinib, both drugs have lower brain penetration and they do not cross blood-brain barrier in significant amounts, and bezuclastinib, in addition, does not inhibit other kinases, such as platelet-derived growth factors.

And in the end, risk versus benefit ratio should be considered for each patient when deciding on tyrosine kinase treatment in non-advanced disease. On one hand, we know that these drugs improve symptoms and improve quality of life, decrease the skin lesions, and decrease the polypharmacy related to anti-mediator treatment. On the other hand, we have to be cognizant of the unknown long-term side effects; they have been safe in short-term with no significant or serious adverse events in the PIONEER trial, at least for avapritinib. But we don't know about the long-term side effects. And reproductive risk should be discussed with the patient because they are contraindicated in pregnancy. And the need for monitoring needs to be adjusted for each patient.

I hope I was able to give you a sense of what patient population might be candidate for tyrosine kinase inhibitor therapies. And I thank you for your attention.

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