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Goals of Therapy for WHIM Syndrome (a Chronic Neutropenic Disorder)

Announcer:

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Dr. Tarrant:

Hi, I'm Terry Tarrant. I'm an Associate Professor of Medicine at Duke University Hospital in the divisions of Rheumatology and Allergy/Immunology. I'll be speaking today on the Goals of Therapy for WHIM Syndrome, which is a Chronic Neutropenic Disorder).

So let's start by talking about neutrophil function. Neutrophils are important because they're the first cells that respond to infections, like bacteria. They rapidly mobilize and migrate from the bone marrow. They release cytotoxic granules to kill the bacteria. They opsonize and then phagocytize that bacteria, and then kill through reactive oxygen species, as well as deploying extracellular NETs to surround and aid in killing bacteria that are larger and can't be engulfed.

So in terms of congenital neutropenia, these are disorders where people have very, very low neutrophils due to a bone maturation arrest in the myeloid lineage. And there are multiple etiologies as to why someone can be neutropenic from a congenital source. They can have inborn errors of immunity, complex inherited syndromic diseases, it can be a metabolic problem, or it could be idiopathic. So as you can see, the reasons for someone to have low or dysfunctional Neutrophils are quite large. But today, we're going to be focusing on a particular disease called WHIM syndrome.

WHIM is an inborn error of immunity, which means that people who have WHIM, have an abnormal copy of the CXCR4 chemokine receptor. It's autosomal dominant, meaning each person in each generation can inherit it with just one bad allele, and it's a gain of function in CXCR4, meaning that the CXCR4 protein is hyper signaling and hyperactive.

In terms of how you recognize WHIM, WHIM has four hallmark features for which it's named. W is for warts; these can be on the hands feet, as well as in the anogenital region. H is for hypogammaglobulinemia, which is low antibodies; these can lead to the I, which are recurrent infections, also being neutropenic from whim can lead to recurrent infections. And then lastly, there is M, or myelokathexis; this is a situation where the neutrophils, in particular, as well as other white blood cells, are trapped inside the bone marrow.

To give you a better idea of what myelokathexis and neutropenia looks like in WHIM, I have a cartoon here that you can see where in WHIM syndrome, if you have an abnormal CXCR4 WHIM mutation, the blood cells are trapped inside the bone marrow, and there are very few in the blood, which leads to neutropenia and lymphopenia. And this is compared to someone who has a normal CXCR4 receptor. And then to actually look at the pathology from patients, as you can see on the left, there's a hypercellular marrow, where you have lots of trapped white blood cells inside, and if you look on the blood, the neutrophils have an abnormal morphology, and there are just very few of them there.

So the important thing for WHIM is to understand that there currently are no FDA approved medications to treat this disease. The current treatments are symptom targeted, and they also can be somewhat preventative now that we have Gardasil as a vaccine to

protect from cervical cancer strains of HPV. So to kind of go over what do we do to treat WHIM syndrome when they have infections, we use antibiotics to treat those infections, and they can be both from neutropenic disorders as well as from having low antibodies. We can use antivirals, if necessary. Immunoglobulin replacement therapy can look different. One is an older form of administration called intravenous immunoglobulin, or IVIg, given monthly, and the other is a subcutaneous infusion of immunoglobulin replacement. This is specifically for WHIM patients who have low antibodies. For those who have normal antibody function, we don't use this medication. G-CSF stands for granulocyte-colony stimulating factor. This is basically a cytokine that allows neutrophils to leave the bone marrow, and it basically blocks the interaction between CXCR4 and its cognate ligand, CXCL12, so that neutrophils can escape. This is used mostly for patients when they are having a severe infection and may be hospitalized and their neutrophil counts are quite low. By using this medication, the neutrophil counts in the blood can be increased, and this hopefully helps to treat infections. It does have a complication of bone pain, so it's not used often. And then lastly, as I mentioned, Gardasil. Gardasil is now being used as a preventative strategy for patients with WHIM to prevent cervical cancer or other forms of HPV-related malignancy, and it is recommended in WHIM, but does need further study.

So in conclusion, our goals of therapy for WHIM are to help treat the symptomatic infections that arise, prevent HPV infections where we can, and to use immunoglobulin replacement therapy when the immunoglobulins are exceptionally low, and this may protect patients from infectious complications.

Thank you.

Announcer:

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