Researchers find cause of severe allergic reaction to cancer drug

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Clinicians have been perplexed by the fact that some patients given the drug cetuximab—an immune-based therapy commonly used to treat persons diagnosed with head and neck cancer, or colon cancer—have a severe and rapid adverse reaction to the drug. Sometimes the reaction includes anaphylaxis, a life-threatening condition characterized by a drop in blood pressure, fainting, difficulty breathing, and wheezing.

Now researchers funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, have discovered that specific pre-existing antibodies cause the severe reaction to the drug. This discovery in turn has enabled them to explain the unusual geographic pattern of this reaction seen among individuals in the United States. The unusual findings of this investigation appear in a report published in the March 13 edition of the *New England Journal of Medicine*.

“These intriguing research findings not only are potentially important to physicians treating certain cancer patients, but also may have broader implications for the use of immunotherapies for other diseases,” notes Anthony S. Fauci, M.D., NIAID director.

NIAID grantee Thomas Platts-Mills, M.D., Ph.D., who heads the Division of Allergy and Clinical Immunology at the University of Virginia, led a research study to investigate the cause of the clinical problem with cetuximab. Their newly reported findings are of immediate importance in the care of cancer patients, says Dr. Platts-

Mills. “Because of the widespread use of cetuximab in cancer treatment, it may be useful to pre-screen patients for specific IgE antibodies to cetuximab to identify those who are at risk for serious adverse reactions, including anaphylaxis.”

Cetuximab is a partially humanized mouse monoclonal antibody, which means it is produced by a single cell line and acts against a specific protein. The drug inhibits a growth factor receptor found on the cell surface, thereby controlling the growth of cancer cells.

Upon reviewing the scientific literature, the research team was intrigued by the unusual geographic distribution of patients with anaphylaxis. For example, 22 percent of patients treated with cetuximab in Tennessee and North Carolina had anaphylactic reactions and even higher rates and clusters of cases were reported from regions of Arkansas, Missouri and Virginia. In contrast, less than 1 percent of patients receiving cetuximab in the Northeast region of the United States suffered such reactions.

Anaphylactic reactions are typically triggered by immunoglobulin E (IgE) antibodies, which the immune system produces after being sensitized by prior exposure to an allergen, a normally harmless substance that in some people causes an abnormal immune response. But when Dr. Platts-Mills and his collaborators further reviewed the clinical data, they came across another unusual finding. Anaphylactic reactions in these individuals had occurred within minutes of their first exposure to cetuximab, suggesting that the patients had already been primed to respond to cetuximab.

The researchers then hypothesized that these patients had pre-existing IgE antibodies that cross-reacted with cetuximab and that these IgE antibodies were directed against a specific sugar molecule present on cetuximab. This hypothesis was derived, in part, from knowledge that all people develop natural antibodies to sugars found on foods, bacteria and

viruses, although such antibodies are of a non-IgE class, called IgM.

To test their hypothesis, Dr. Platts-Mills and his colleagues analyzed the antibodies present in serum of 538 individuals. They developed a technique for measuring IgE antibodies to cetuximab and, in further experiments, proved that the IgE antibodies were directed against sugar molecules on cetuximab.

The 538 serum samples included pre-treatment samples taken from 76 cetuximab-treated cancer patients primarily from Tennessee, Arkansas and North Carolina. The remaining serum samples—from individuals in Nashville, Northern California and Boston—served as controls to investigate the geographical differences in hypersensitivity rates.

The researchers found that among the 76 cancer patients, 25 developed hypersensitivity reactions and 18 of these individuals showed a positive reaction for IgE antibodies to the drug. Among the 51 serum samples from patients who did not have a hypersensitivity reaction, only one had such antibodies. In control groups, IgE antibodies against cetuximab were found in 21 percent of the samples from Nashville, 6 percent of the samples from Northern California, and less than 1 percent of the samples from Boston.

Although severe anaphylactic reactions have been reported following treatment with several different monoclonal antibodies, this is the first time a clear mechanism underlying such a reaction has been defined. “Dr. Platts-Mills and his colleagues have shown that the presence of pre-existing IgE antibodies to a specific sugar molecule on cetuximab is highly predictive of a hypersensitivity reaction to cetuximab,” says Marshall Plaut, M.D., chief of the Allergic Mechanisms Section at NIAID. “Furthermore, their research answers an important question about how the local geographic prevalence of these antibodies leads to regional differences in anaphylactic reactions to cetuximab.”

Now the researchers are looking for answers to yet another question: What causes a high proportion of the population in certain parts of the country to produce these particular IgE antibodies that react with cetuximab? Research is in progress to explore if the specific IgE antibodies are triggered by differences in regional exposures to ticks or other parasites or to infectious organisms.

Source: National Institute of Allergy and Infectious Diseases