Cytokine levels could predict immunotherapy problems

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From left, Dr. Wakeland, Dr. Gerber, and Dr. Khan are seeking predictors for patients who will develop autoimmune reactions to cancer immunotherapy. Credit: UT Southwestern

The development of immunotherapy, which mobilizes the body's own immune system to destroy cancer cells, is one of the greatest advances in cancer treatment, but immunotherapy can cause harm to healthy tissue in some patients. Researchers at UT Southwestern have identified blood-based biomarkers that may help identify those patients at greatest risk of developing autoimmune side effects from the treatment.

The researchers found that levels of certain cytokines—molecules that signal parts of the immune system to ramp up—were particularly low before treatment in patients who developed immune-related adverse events. Further, these patients also showed greater increases in cytokine levels immediately after treatment was started than patients who did not develop problems.

The findings, published in the *British Journal of Cancer*, suggest that patients at high risk for complications from immunotherapy may have pre-existing immune-regulation problems.

What is immunotherapy?

- Immunotherapy is a type of cancer treatment that uses the patient's own immune system to fight the cancer. Over the past decade, it has become widely used to treat certain types of cancer.
- Immunotherapy is approved to treat melanoma, lung cancer, kidney cancer, certain gastrointestinal cancers, liver cancer, lymphoma, and childhood leukemia.
- Checkpoint inhibitors, the most commonly used type of immunotherapy, work by taking the "brakes" off the immune system. Checkpoint inhibitors are administered intravenously every two to six weeks.

"Almost a decade into the remarkable era of cancer immunotherapy,

immune-related adverse events continue to plague patients and puzzle clinicians," said senior author Dr. David Gerber, Professor of Internal Medicine and Clinical Sciences and Associate Director for Clinical Research in the Harold C. Simmons Comprehensive Cancer Center. "While some of these toxicities, such as rash and thyroid dysfunction, can be easily managed, others such as pulmonary toxicity may result in hospitalization and even ICU-level care. Identifying these cytokines and other biomarkers for the prediction and tracking of autoimmune toxicity could help us customize immunotherapy, tailor monitoring and increase patient safety, and possibly even expand the use of immunotherapy to populations that are currently excluded."

Dr. Gerber said their study included patients with a variety of cancer types. "Earlier studies of immune-related adverse events focused almost exclusively on melanoma patients, who are often treated with types of immunotherapy not used in other cancers. Our study enrolled a variety of patients with different cancer types and who were treated with widely used immunotherapy drugs."

With a grant from the American Cancer Society and the Melanoma Research Alliance, this research will be expanded to a large, multicenter clinical trial that will look at a variety of potential biomarkers that can predict the autoimmune effect.

The published pilot study included 65 patients and 13 healthy controls who were evaluated for levels of 40 cytokines before treatment and two times following treatment. The forthcoming multicenter clinical trial will enroll 600 patients and include evaluations of 130 auto-antibodies; genetic tests for genes associated with autoimmune and inflammatory diseases; and functional tests, including cytokines. Blood samples will be taken before treatment, about six weeks after immunotherapy is started, and at the time of an immune-related adverse event, if one occurs.

Dr. Edward Wakeland, Professor of Immunology and a co-author, said the results of the study are an initial step toward greater understanding of the adverse events that occur with immunotherapy.

"Regulating the immune system is extremely complex, and a variety of patient-specific factors, including genetic predisposition, humoral immunity, interactions with the microbiome, and functional activation all play important roles in determining whether a beneficial or detrimental immune response develops. Nevertheless, our initial findings bode well for ultimately developing patient-specific strategies for effective and safe cancer immunotherapy," said Dr. Wakeland, who holds the Edwin L. Cox Distinguished Chair in Immunology and Genetics.

"The key finding is that there is some sort of underlying immune dysregulation in patients who develop autoimmune toxicities. Ongoing studies are focused on utilizing immune monitoring, immunogenomics, and single-cell genomics strategies in identifying biomarkers and understanding the mechanisms underlying immune-related adverse events in larger patient populations," said Dr. Shaheen Khan, Instructor of Immunology and first author of the study.

More information: Shaheen Khan et al, Immune dysregulation in cancer patients developing immune-related adverse events, *British Journal of Cancer* (2018). DOI: 10.1038/s41416-018-0155-1

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