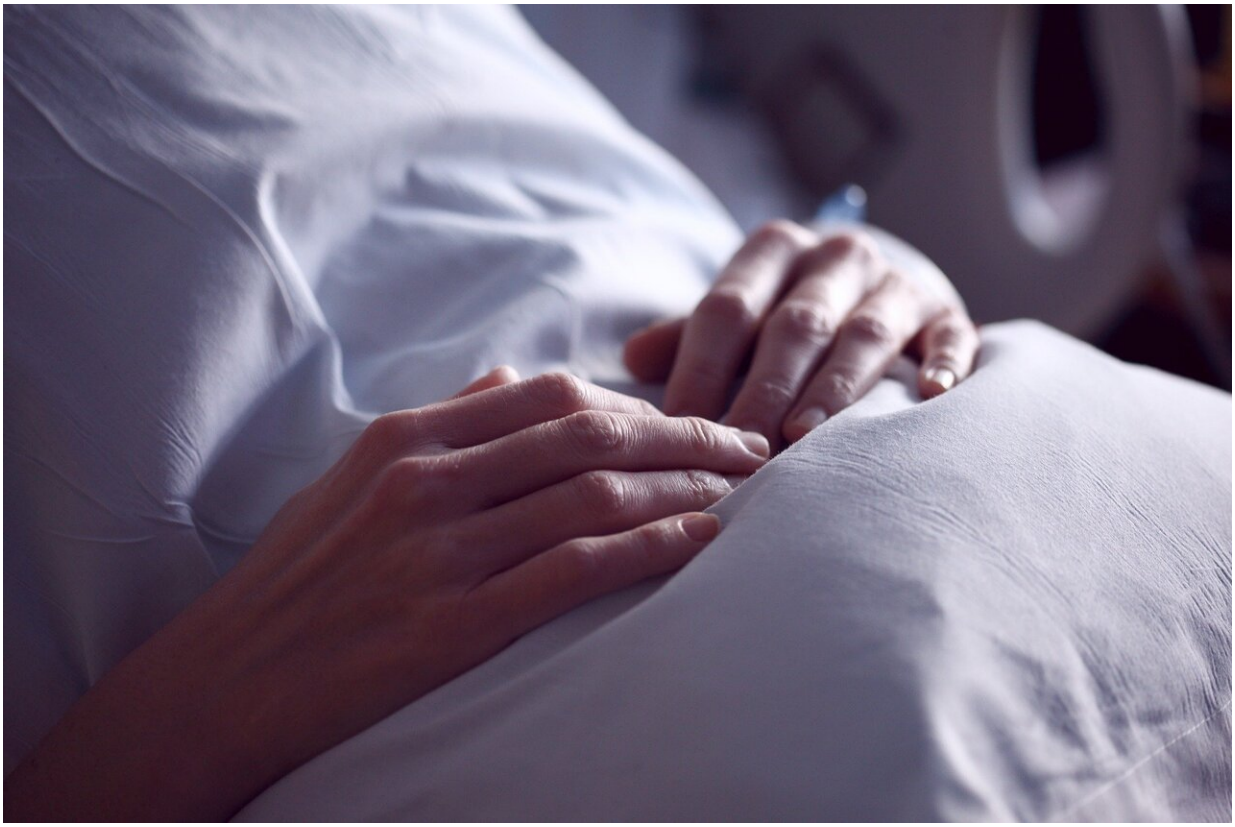
Researchers identify factors to predict severe toxicities in CAR T patients

July 15 2020



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Chimeric antigen receptor T-cell therapy (CAR T) has proved to be a valuable treatment option for patients with lymphoma who have failed other therapies. In clinical trials, the cellular immunotherapy was shown

to provide durable remissions for nearly 40% of large B cell lymphoma patients. Despite its success, CAR T may not be the best option for all patients due to their cancer prognosis and the risk for developing severe toxicities or treatment-related death. In a new study published in *Clinical Cancer Research*, Moffitt Cancer Center researchers identify possible factors that could help physicians know if patients are at higher risk for severe adverse events before they receive CAR T therapy.

The development of immune-mediated toxicities, such as cytokine release syndrome and neurotoxicity, remains a common challenge of CAR T therapy. For this therapy, a patient's own T cells are removed, re-engineered in a lab and infused back into the patient. The new army of immune cells are designed to seek out and attack cancer cells. But that immune boost can cause large amounts of cytokines to be released into the blood, which can cause a patient to develop a fever, increased heart rate, difficulty breathing or low blood pressure.

"Identifying which CAR T patients may be more susceptible to those severe toxicities before therapy could allow us to better tailor their care to mediate or reduce those adverse reactions," said Marco Davila, M.D., Ph.D., study corresponding author, associate member of the Blood and Marrow Transplant and Cellular Immunotherapy Department and medical director of Cell Therapies at Moffitt.

To better understand what may put a patient at higher risk for toxicities, the Moffitt researchers followed 75 patients with large B cell lymphoma who were treated with the CAR T cell product axicabtagene ciloleucel (Yescarta) as the standard of care. Levels of serum cytokine and catecholamine, a type of neurotransmitter, were measured before receiving lymphodepleting chemotherapy prior to treatment, on the day of their CAR T infusion and daily thereafter during their hospitalization. Tumor biopsies were also performed before treatment to analyze gene expression of the tumor and its microenvironment.

The researchers found that increased levels of pre-treatment with interleukin 6, an inflammatory molecule, indicated a high risk for neurotoxicity and cytokine release syndrome from CAR T therapy. This group also had an elevated risk of death from the treatment. "These patients experienced significant toxicities despite management with early cytokine-blockade and steroids," said Rawan Faramand, M.D., lead study co-author and assistant member of the Blood and Marrow Transplant and Cellular Immunotherapy Department at Moffitt.

Tumor gene expression data showed myeloid cells and regulatory T cells may also play an important role in the development of neurotoxicity and cytokine release syndrome. The researchers believe the interaction between infused CAR T cells and the recipient's immune cells may determine the severity of the toxicities and suggest further studies on reducing inflammation and targeting the tumor microenvironment prior to therapy.

More information: Donghua Shi et al. Chimeric Antigen Receptor-Glypican-3 T-Cell Therapy for Advanced Hepatocellular Carcinoma: Results of Phase I Trials, *Clinical Cancer Research* (2020). DOI: 10.1158/1078-0432.CCR-19-3259

Provided by H. Lee Moffitt Cancer Center & Research Institute