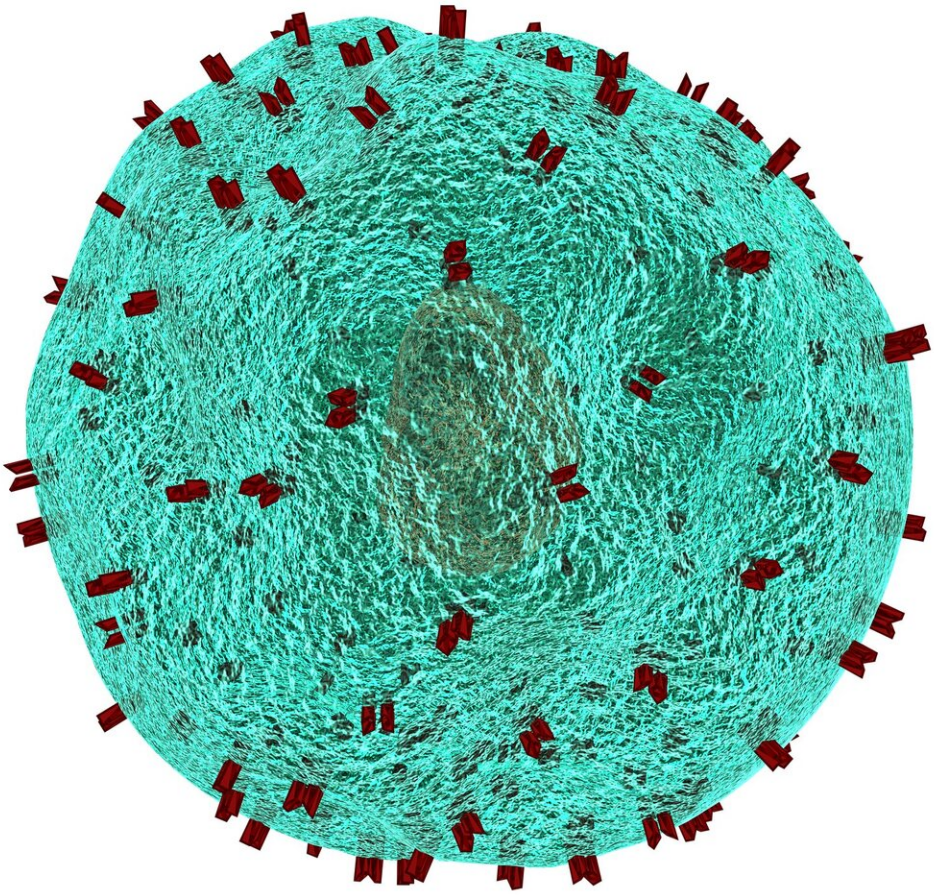
Study identifies characteristics of infused CAR T cells in patients with large B-cell lymphoma

October 5 2020



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Researchers at The University of Texas MD Anderson Cancer Center have identified molecular and cellular characteristics of anti-CD19 CAR T cell infusion products associated with how patients with large B-cell lymphoma (LBCL) respond to treatment and develop side effects.

The research team also found that early changes in circulating tumor DNA one week after CAR T cell therapy may be predictive of treatment response in a particular patient. The paper was published online today in *Nature Medicine.*

"CAR T cell therapy is highly effective against LBCL," said corresponding author Michael Green, Ph.D., associate professor of Lymphoma and Myeloma. "However, we experience two main clinical challenges: achieving long-term remission and managing treatment-associated adverse events."

This study suggests that, within the first week of therapy, clinicians may be able to identify a subset of patients who may experience more poor outcomes or adverse treatment reactions, said Green. This would allow the care team to adjust therapy to improve efficacy or to act to mitigate toxicity.

CAR T cell signature, early molecular response may predict long-term outcomes

For this study, researchers performed single-cell analysis on CAR T cells

to study gene expression profiles in the infused cells. CAR T cells were collected from those remaining in infusion bags following treatment of 24 patients with LBCL. These genetic profiles were compared to treatment responses, determined at three months post-infusion by PET/CT scan.

"When we look at the characteristics of the infused CAR T cells, we found that samples from patients who were less responsive to treatment had exhausted T cells, whereas those who experienced complete responses had T cells expressing 'memory' signatures," said co-corresponding author Sattva Neelapu, M.D., professor of Lymphoma and Myeloma. "Additionally, one cellular signature of T cell exhaustion was more commonly found in patients who exhibited a poor molecular response, and poor molecular response is generally associated with less-positive, long-term outcomes."

Further, the researchers analyzed early molecular responses in the patients by monitoring changes in circulating tumor DNA from treatment to one week post-infusion. The magnitude of change in tumor-associated DNA corresponded with response, suggesting that patients who displayed an early molecular response were more likely to experience a clinical response to treatment.

CAR T cell features predict likelihood of severe side effects

Adverse side effects of CAR T cell therapy can include cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS). These adverse events can delay patients' recovery and can lead to increased need for hospitalization and intensive care.

"When we examined the infusion product, we found that a cell

population with characteristics similar to myeloid cells, with a monocyte-like transcriptional signature, was associated with development of high-grade neurotoxicity," said Green. "Detecting these cells may subsequently lead us to identify patients who would be at higher risk of developing neurotoxicity, allowing us to provide prophylactic treatment with agents that target the specific cellular features."

Further examination may lead to insights into the types and attributes of the cells present within the CAR T infusion product.

"This study also tells us that some rare and unexpected cells identified by single-cell analysis could be biologically important," said co-corresponding author Linghua Wang, M.D., assistant professor of Genomic Medicine. "Going forward, we plan to functionally characterize these monocyte-like cells to better understand their specific biological mechanisms driving these clinical results."

These findings will help researchers develop clinical interventions that can block or target these cells. They also plan to validate the capacity of circulating tumor DNA to accurately predict patients' long-term outcomes.

More information: Deng, Q., Han, G., Puebla-Osorio, N. et al. Characteristics of anti-CD19 CAR T cell infusion products associated with efficacy and toxicity in patients with large B cell lymphomas. Nat Med (2020). doi.org/10.1038/s41591-020-1061-7 , www.nature.com/articles/s41591-020-1061-7

Provided by University of Texas M. D. Anderson Cancer Center