Low blood phosphate levels may be linked to neurological side effects from CAR T-cell therapy

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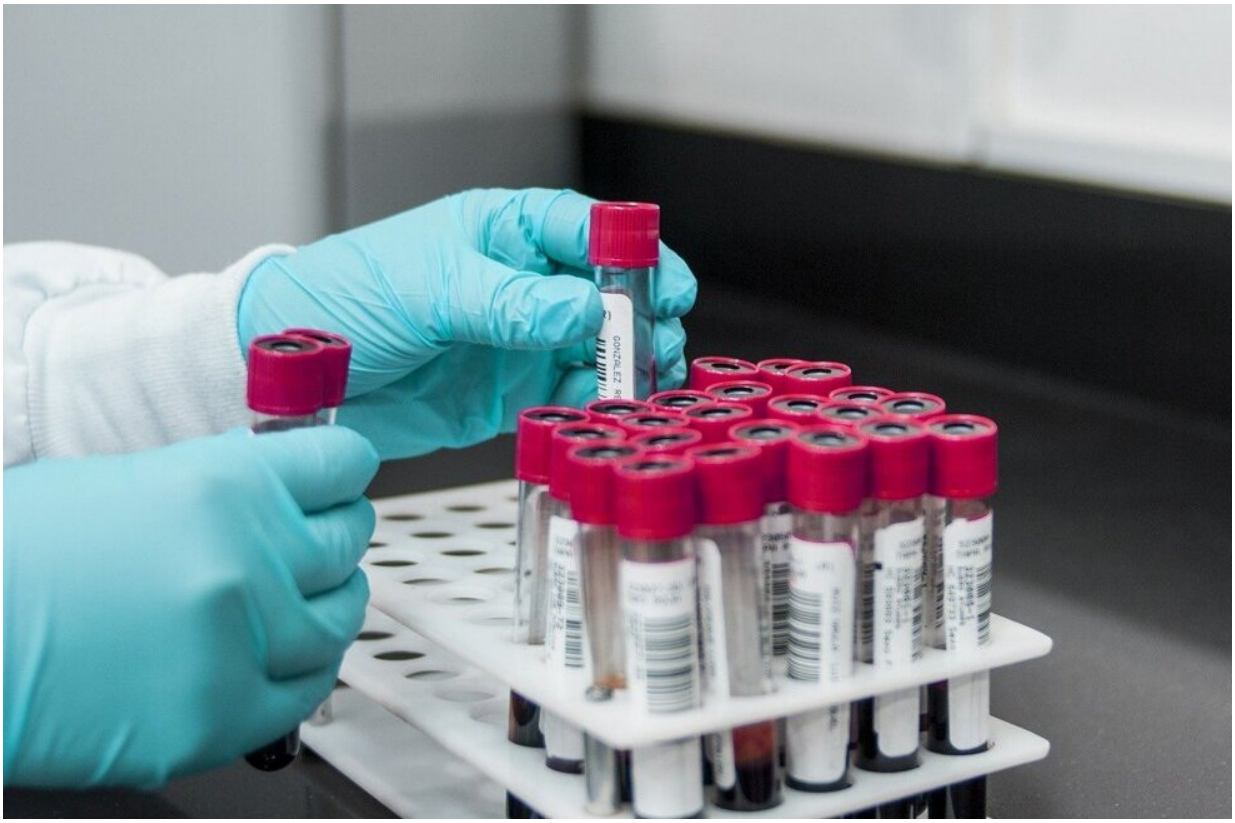

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Incidence and severity of neurological side effects from chimeric antigen receptor (CAR) T-cell therapy were higher in patients who had

hypophosphatemia (low blood phosphate levels), according to results published in *Cancer Immunology Research*.

Neurological toxicity associated with CAR T-cell therapy, known as immune effector cell-associated neurotoxicity syndrome (ICANS), affects approximately 50% of recipients. Symptoms include confusion, delirium, aphasia, impaired motor skills, and somnolence. In severe cases, life-threatening events, including seizures and coma, can occur.

"The treatment of ICANS is currently limited to supportive care and steroids, which are nonspecific and can have their own side effects," said Theodore Scott Nowicki, MD, Ph.D., assistant professor-in-residence in the Departments of Pediatrics (Hematology/Oncology) and Microbiology, Immunology, & Molecular Genetics at the David Geffen School of Medicine, UCLA, and lead author of the study. "Therefore, having the ability to predict the onset of ICANS would be a very helpful tool for clinicians."

The authors had previously observed a marked drop of phosphate levels in the blood of patients receiving CAR T-cell therapy in the days following the cell infusions. Notably, the timing of this effect overlapped with when the patients developed ICANS. Neurological symptoms of hypophosphatemia and ICANS are similar, Nowicki explained.

In this study, Nowicki and colleagues explored the relationship between hypophosphatemia and ICANS incidence, as well as the putative mechanism behind the low phosphate levels.

The researchers co-cultured lymphoma cells expressing the CD19 antigen with CD19-targeted CAR T cells and found that lymphoma cell killing was associated with reduced phosphate concentrations in the culture media. Furthermore, CAR T cells co-cultured with lymphoma cells consumed significantly more phosphate than when cultured alone.

The increased phosphate consumption of CAR T cells correlated with their activation following CD19 antigen recognition—as shown by increased cytokine release—and with elevated phosphate-dependent metabolic activity. These findings indicate that CAR T cell–mediated cell killing results in heightened metabolic demand that could drive hypophosphatemia in patients.

To test this hypothesis, the authors conducted a retrospective analysis of a clinical cohort of 77 patients with B-cell malignancies treated at UCLA with CD19-targeted CAR T-cell therapy.

In this cohort, 30% of the patients developed ICANS, and approximately 60% had hypophosphatemia (defined as serum phosphate concentrations lower than 2mg/dL). Although the serum levels of potassium and magnesium were also low in 52% and 72% of the patients, respectively, only low phosphate was significantly associated with ICANS, with most patients who developed ICANS (91%) also displaying hypophosphatemia. In addition, the patients had the lowest phosphate concentrations five days post-CAR T cell infusion, which coincided with the median time to onset of ICANS.

"While some patients who experienced hypophosphatemia did not develop ICANS, we found that the patients with ICANS consistently had more severe degrees of hypophosphatemia," said Nowicki. "Furthermore, among patients with low phosphate levels, the severity of hypophosphatemia correlated with the severity of the ICANS that they developed."

The authors did not observe a significant difference in ICANS severity between patients who had hypophosphatemia and those who did not. However, patients with low phosphate levels experienced significantly longer duration of ICANS than patients with phosphate levels within normal range.

"With larger sample sizes or meta-analyses from other studies in the future, we may be able to detect changes in severity more sensitively," Nowicki added.

These findings could have implications for monitoring for the development of ICANS in patients receiving CAR T-cell therapies for cancer. "Clinicians could potentially utilize serum phosphate measurements, which are regularly tested in patients receiving CAR T-cell products, to help predict when they are at greater risk for developing ICANS," said Nowicki.

According to the authors, the key limitation of this study was the inability to prospectively study whether hypophosphatemia in fact caused ICANS. "I think this is an important future question to address," said Nowicki. "My group is continuing to actively study this potential connection. If confirmed, it would have significant implications for how ICANS is managed in patients receiving cell therapy."

More information: Jack Pengfei Tang et al, Hypophosphatemia Due to Increased Effector Cell Metabolic Activity Is Associated with Neurotoxicity Symptoms in CD19-Targeted CAR T-cell Therapy, *Cancer Immunology Research* (2022). DOI: 10.1158/2326-6066.CIR-22-0418

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