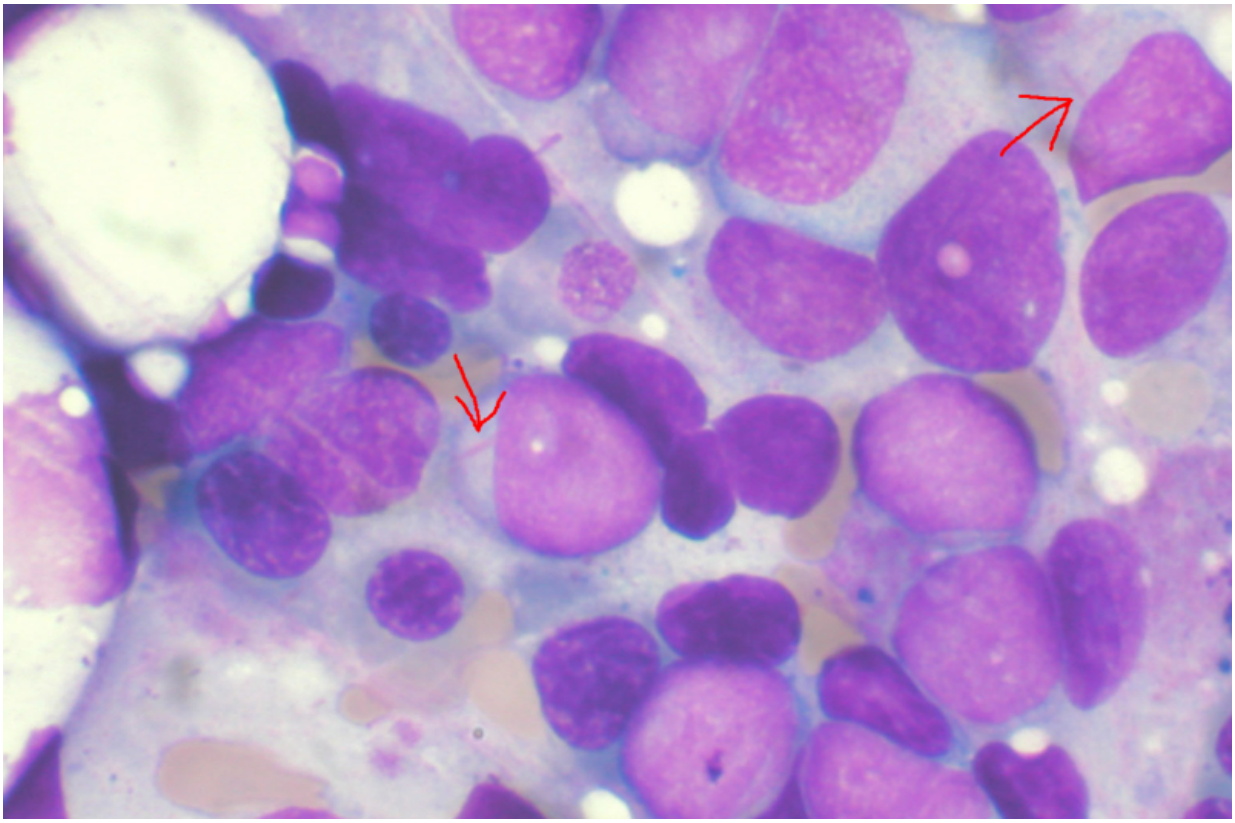
Engineered safety switch curbs severe side effects of CAR-T immunotherapy

March 4 2021



Bone marrow aspirate showing acute myeloid leukemia. Several blasts have Auer rods. Credit: Wikipedia

UNC Lineberger Comprehensive Cancer Center researchers have successfully used an experimental safety switch, incorporated as part of

a chimeric antigen receptor T-cell (CAR-T) therapy, a type of immunotherapy, to reduce the severity of treatment side effects that sometimes occur. This advance was seen in a patient enrolled in a clinical trial using CAR-T to treat refractory acute B-cell leukemia. It demonstrates a proof-of-principle for possible expanded use of CAR-T immunotherapy paired with the safety switch.

The researchers published their findings in the journal *Blood* as an ahead-of-print publication.

With CAR-T therapy, T-cells from a patient's immune system are modified in a manufacturing facility to express part of an antibody that can bind to a surface protein on cancer cells. The modified T-cells, after being infused back into the patient, seek out and attack cancer cells throughout the body. Patients with leukemia or lymphoma have experienced complete remission when treated with CAR-T therapy but sometimes experience toxicities, which can be life-threatening, due to inflammatory responses or nervous system toxicities caused by the modified T-cells.

When using standard forms of cancer therapies, including pills and infused drugs, doctors can interrupt or lower drug dosing to respond to treatment toxicities. With cell-based immunotherapies, this is not possible after the cells are infused. So UNC Lineberger researchers engineered T-cells to include a safety switch, called inducible caspase-9, or iC9, that can be activated if toxic side effects develop. Administration of the drug rimiducid 'triggers' the switch to activate the expression of caspase-9, potentially leading to reduced severe side effects from the CAR-T therapy.

"Because of our active Cellular Immunotherapy Program at UNC Lineberger, we can engineer and generate various CAR-T cells for clinical trials. In this case, we have produced specialized CAR-T cells

that could benefit patients by enhancing safety," said Matthew Foster, MD, lead author of the study and an associate professor in the UNC School of Medicine and a UNC Lineberger member. "With the assistance of our partner Bellicum Pharmaceuticals, we collaborated to use the safety switch-triggering drug rimiducid with cells manufactured at UNC Lineberger."

UNC Lineberger has enrolled patients in an ongoing early-phase clinical trial to determine whether a novel CAR-T therapy with the iC9 safety switch is safe and effective against relapsed or refractory B-cell acute lymphoblastic leukemia, a difficult to treat, fast-moving cancer that occurs frequently in children, adolescents and young adults.

One of the participants in the study, a 26-year-old woman, experienced a severe side effect—immune effector cell-associated neurotoxicity syndrome (ICANS)—after being infused with CAR-T. Her clinicians quickly reduced the severity of the side effects by administering the drug rimiducid to activate the iC9 safety switch. As intended, Foster said the safety switch reduced the number of circulating modified T-cells by nearly 60 percent within four hours and by more than 90 percent within 24 hours. The drug nearly eliminated the toxicities within one day.

"Even though this case study only documents an outcome in one patient, the fact that the drug was so successful so quickly gives us hope that it could have wider applications in a larger group of leukemia patients," said Gianpietro Dotti, MD, director of the UNC Lineberger Cellular Immunotherapy Program and professor of medicine at the UNC School of Medicine. "It should be noted that while rimiducid mitigated her toxicities, it also lowered the number of iC9 T cells fighting her cancer by 90 percent. But there seemed to be sufficient T-cells still circulating to maintain an anticancer response."

This trial is ongoing but the investigators will next explore the effects of

lower doses of rimiducid in patients with less severe toxicity as it could be a way to intervene early and prevent severe toxicity.

"Given these results and the well-established high response rates in B-cell acute lymphoblastic leukemia patients receiving CAR-T cells, it is reasonable to have a high bar in 2021 and expect that we can achieve both safety and efficacy from such therapies," concluded Foster.

The investigators also see the potential to use CAR-T designed with the built-in safety switch to treat other cancers. "The ability to use a safety switch may also allow us to treat patients with solid tumors where there may be concern about the CAR-T cells affecting non-cancer tissue," said Jonathan Serody, MD, director of the UNC Lineberger Cellular Therapy Program. "In those instances, side effects can be eliminated by activating the safety switch."

More information: Matthew C Foster et al, Utility of Safety Switch to Abrogate CD19.CAR T Cell-Associated Neurotoxicity, *Blood* (2021). DOI: 10.1182/blood.2021010784

Provided by UNC Lineberger Comprehensive Cancer Center