Off-the-Shelf CAR-NK Cell Therapy Elicits Leukemia Remission

Engineered natural killer cells with logic gates led to complete remission of relapsed or refractory acute myeloid leukemia.

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Off-the-Shelf CAR Natural Killer Cell Therapy with Logic Gates Elicits Complete Remissions in Relapsed or Refractory Blood Cancers

Several patients with acute myeloid leukemia (AML), who were treated with SENTI-202, a first-in-class chimeric antigen receptor natural killer (CAR NK) cell therapy, experienced a complete remission after not responding to or having relapsed following prior treatments, according to interim results from the phase I SENTI-202-101 clinical trial presented at the American Association for Cancer Research (AACR) Annual Meeting 2025, held April 25-30.

CAR T-cell therapy has shown success in the treatment of B-cell malignancies, including multiple myeloma and some B-cell leukemias and lymphomas. However, some characteristics of AML and other blood cancers make them more challenging to treat with conventional drugs, such as cell-based therapies and antibodies, according to Stephen Strickland, Jr., MD, MSCI, director of leukemia research for Sarah Cannon Research Institute, who presented the study.

Firstly, AML is a heterogeneous disease, which can complicate efforts to find a consistent target.

“There is no single target that is uniformly expressed across heterogeneous AML cells, and many targets that are potentially targetable in AML are also expressed on healthy cells,” Strickland said.

Further, all CAR T-cell therapies currently approved by the U.S. Food and Drug Administration (FDA) consist of cells harvested from the patient, engineered in a laboratory to target cancer cells, and infused back into the patient. This process takes time that patients with rapidly progressing cancers like AML might not have, especially if their cancer has already progressed during or following treatment with another agent, Strickland said.

Moreover, AML patients often have dysfunctional T cells, which can lead to manufacturing challenges, he added.

To overcome these challenges, researchers leveraged the unique properties of natural killer (NK)

cells, another type of immune cell, to design a different cell therapy. Like T cells, NK cells can be engineered with a CAR to target cancer cells. But unlike currently approved CAR T cells, CAR NK cells can be made from healthy donor cells and stored for future use, making them available as "off-the-shelf" treatments that can reach patients quickly. CAR NK cells may cause fewer immune-related side effects than CAR T cells as well, Strickland explained.

The CAR NK cell therapy SENTI-202 employed the concept of logic gating in the design of their CAR NK cells to improve specificity and reduce toxicity. The cells recognize two different targets, CD33 and FLT3, on AML cells, which may broaden their reach in a heterogeneous population by targeting cells that express either protein. The CAR NK cells also contain an inhibitory receptor that prevents them from killing healthy cells that may express CD33 and/or FLT3 if these healthy cells also express EMCN, a protein found on normal hematopoietic stem cells.

"Unlike antibody-drug conjugates or bispecific antibodies, this sort of logic-gating behavior can only be implemented in cell therapies and is a potentially unique way to treat AML by overcoming tumor heterogeneity and sparing healthy cells," Strickland said.

Strickland and colleagues are testing the safety, dosing, and preliminary efficacy of SENTI-202 in the first-in-human, phase I SENTI-202-101 clinical trial. As of the data cut off, nine patients with relapsed or treatment refractory AML have received at least one cycle of SENTI-202.

The patients underwent lymphodepleting chemotherapy before infusion with three to five doses of 1 billion or 1.5 billion CAR NK cells given in 28-day cycles. No dose-limiting toxicities were observed, and the maximum tolerated dose was not reached. The preliminary recommended phase II dose was established as three doses of 1.5 billion cells per cycle.

At the time of analysis, seven of nine patients were evaluable for best overall response, with the remaining two continuing on treatment after experiencing AML disease reduction with the first cycle. Four of the seven patients experienced a complete remission, all with no evidence of measurable residual disease (three with full and one with partial hematologic recovery), and a fifth patient experienced a morphologic leukemia-free state (blast reduction below 5% without platelet and neutrophil count recovery). All complete responses were ongoing with a maximum follow-up time of over eight months, and three patients received a bone marrow transplant after treatment with SENTI-202.

Four patients each reported grade 3 or higher febrile neutropenia and decreased platelet count, and two patients each reported grade 3 anemia and abdominal pain, but these side effects were either deemed unrelated to SENTI-202 or resulting from the lymphodepleting chemotherapy in all patients except one. No grade 5 adverse events were observed.

"The deep and durable responses observed in patients for whom we have follow-up data are impressive," Strickland said. "We are hopeful this can be a new type of treatment for AML patients where the unmet medical need is extremely high."

While the results are preliminary, Strickland finds them encouraging and hopes this study will open

more doors for the use of logic-gated cell therapies in other cancer types, including solid tumors. “There are very few ‘clean’ cancer targets that are only expressed on cancer cells but not on healthy cells,” he said. “The logic-gating technology potentially solves this issue by recognizing one or more cancer targets to trigger deeper cancer killing while recognizing healthy cells to prevent them from being affected.”

Limitations of this study include its small sample size, short follow-up time, and lack of direct comparisons to existing treatments. The study continues to enroll additional patients at the preliminary recommended phase II dose to further evaluate the safety and efficacy of SENTI-202.

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