Natural Killer Cells Show Promise as a New Type of Immunotherapy

Two treatment approaches using donor or engineered NK cells led to remission in people with lymphoma and leukemia.

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Two approaches using natural killer (NK) cells show promise for treating people with blood cancers. One approach, using NK cells from umbilical cord blood combined with a bispecific antibody, led to remission in 89% of patients with Hodgkin lymphoma, according to research presented at the American Association for Cancer Research Annual Meeting (AACR 2022). In addition, Nkarta recently announced that two off-the-shelf CAR-NK cell therapies produced good responses in more than half of people with advanced leukemia or lymphoma.

Natural killer cells, one of several types of immune system white blood cell, act as sentinels to ferret out malignant and virus-infected cells. While T cells are most commonly used for immunotherapy, NK cells also play a role in fighting cancer. But unlike T cells, NK cells do not have to be customized for each patient, and they are less likely to cause severe side effects.

NK Cells Plus Bispecific Antibody

As reported at AACR 2022, researchers tested NK cells derived from umbilical cord blood collected soon after birth. The NK cells were activated with cytokines and attached to a bispecific antibody that targets CD30 and CD16A. The antibody, dubbed AFM13, binds to both the CD30 receptor on lymphoma cells and the CD16A receptor on NK cells, creating a “bridge” that enables the killer cells to attack the cancer.

This Phase I/II clinical trial included 22 patients with relapsed or refractory CD30-positive lymphoma (mostly Hodgkin lymphoma). They had all received prior treatment with the antibody-drug conjugate Adcetris (brentuximab vedotin) and all but one had tried a checkpoint inhibitor. Most had undergone a stem cell transplant, and two had even received CAR-T therapy without success.

The patients first underwent strong conditioning chemotherapy to kill off existing immune cells and make room for new ones. Then they received two infusions of 1 million, 10 million or 100 million of the NK-antibody complexes; the highest dose will be used for future trials. They later received three additional infusions of AFM13 alone.

People treated with the combination therapy had a 89% overall response rate (17 of 19 treated patients), including 10 with complete remission and seven with partial responses. But among the 13 participants who received the highest dose, the overall response rate was 100%, including eight (62%) with complete responses.

After a median follow-up of nine months, the progression free survival rate across all dose levels was 52%, and the overall survival rate was 81%, rising to 67% and 93%, respectively, for those treated with the highest dose. Several patients went on to receive stem cell transplants.

Treatment was generally safe. While patients did experience hematological toxicity, or blood cell depletion due to the conditioning therapy, the researchers observed no adverse events related to the NK cells and just one severe adverse event due to a follow-up AFM13 infusion. There were no cases of cytokine release syndrome, neurotoxicity or graft-vs-host disease.

“We were favorably surprised by the quality of tumor responses in patients who had resistant lymphomas, some of whom were in a very poor condition at enrollment,” presenter Yago Nieto, MD, PhD, of the University of Texas MD Anderson Cancer Center, said in an AACR press release. “We hope that this new therapeutic option can potentially be used as a bridge to stem cell transplantation or perhaps even as a curative treatment and will bring hope to this patient population with a large unmet need.”

These response rates are “staggering,” and the tolerability profile is “truly excellent,” Timothy Yap, MBBS, PhD, of MD Anderson Cancer Center, said at an AACR press briefing. “Everyone can see for themselves how impressive these results are.”

CAR-NK Cells
On April 25, the biopharmaceutical company Nkarta announced positive results from a pair of small Phase I trials evaluating two off-the-shelf CAR-NK therapies for the treatment of leukemia and lymphoma.

Following on the success of chimeric antigen receptor T-cell therapy—better known as CAR-T—scientists have developed CAR-NK cells that are genetically reprogrammed using artificial receptors that bind to cancer cells. Unlike CAR-T therapy, which involves modification of cells collected from each individual patient, CAR-NK cells can be mass produced from donor cells and frozen, which saves time and hopefully will be less costly.

In the first study, researchers evaluated a CAR-NK product called NKX101 in 17 people with relapsed or refractory acute myeloid leukemia (AML) and four with myelodysplastic syndrome. NKX101 contains an engineered receptor that targets NKG2D molecules on malignant cells, which are recognized by NKG2D receptors on NK cells.

The participants received three infusions of NKX101 using different dose levels. Three of the five AML patients (60%) treated with the two highest doses (1 or 1.5 billion CAR-NK cells) achieved a complete response, and two of them were negative for minimal residual disease, a more stringent measure of response. None of the patients with myelodysplastic syndrome responded.

The second study evaluated a different product called NKX019 in 13 people with relapsed or refractory B-cell malignancies, mostly non-Hodgkin lymphoma (NHL). NKX019 contains an engineered receptor that targets CD19 on B-cells—a common target of CAR-T and other existing therapies—as well as a form of interleukin-15 to enhance cell persistence and activity.

These participants also received three infusions using different dose levels. The overall response rate for NHL patients across all doses was 70%; however, none of the patients with acute lymphoblastic leukemia responded. Among those treated with the high dose (1 billion CAR-NK cells), five of six NHL patients (83%) experienced remission, including three (50%) with complete responses. No relapses have been seen to date.

In both studies the treatments were safe and generally well tolerated. There were no-dose limiting toxicities, and patients did not experience the types of adverse events sometimes seen with CAR-T therapy. Again, there were no cases of cytokine release syndrome, neurotoxicity or graft-vs-host disease.

“We’re excited to see our CAR NK co-lead candidates, NKX101 and NKX019, show such striking early single-agent activity in heavily pretreated patient populations, with an exceptional safety profile without the side effects associated with CAR T cell therapies,” Nkarta president and CEO Paul Hastings said in a company press release. “These encouraging data across multiple indications further validate Nkarta’s best-in-class NK cell platform, as we seek to transform cancer treatment by bringing together the safety advantages of NK cells with an off-the-shelf modality designed to make the benefits of cell therapy accessible in a community setting.”

Click here to read the AACR2022 study abstract.
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