ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Development of Chimeric Antigen Receptor Natural Killer–Cell Therapy

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H&O What is chimeric antigen receptor natural killer (CAR NK)-cell therapy?

KR Most people are familiar with the groundbreaking work done with CAR T-cell therapy, which has shown remarkable success in treating hematologic malignancies. In CAR NK-cell therapy, another form of immunotherapy, NK cells, an important component of the innate immune system, are engineered ex vivo to express a CAR. This modification enables NK cells to recognize and eliminate cancer cells more effectively.

H&O What makes CAR NK-cell therapy different from CAR T-cell therapy?

KR NK cells, which are part of the innate immune system, have certain unique characteristics that make them particularly attractive for cell therapy. They are naturally capable of recognizing virally infected cells and abnormally stressed cells, such as cancer cells. What makes them especially well-suited to cell therapy is that unlike CAR T cells, NK cells in the allogeneic setting do not cause graft-versus-host disease, so that they can be safely administered from a healthy donor to a patient.

The US Food and Drug Administration has approved 7 CAR T-cell products, all of which are autologous. Manufacturing a patient-specific product from a patient's own cells adds notable complexity and cost to the treatment. In addition, CAR T-cell therapy carries a risk of toxicities that are not commonly observed with NK-cell therapy—namely, severe cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). Another advantage of CAR NK-cell therapy is its potential to be used as an off-the-shelf product. Cells from one healthy donor can be used to manufacture dozens or even hundreds of doses that can be frozen and available for use as needed. This feature can reduce the cost of treatment dramatically.

H&O In which types of cancer has CAR NK-cell therapy been tested?

KR CAR NK cells have been tested in clinical trials for hematologic malignancies and are now being tested in an increasing number of solid tumors, including ovarian cancer, pancreatic cancer, glioblastoma, colorectal cancer, breast cancer, renal cell carcinoma, and osteosarcoma. Although most of these trials are still in early phases, the field is expanding rapidly.

H&O How is the treatment administered?

KR CAR NK cells are usually administered intravenously, like a blood transfusion. We have noticed that for certain types of cancer, however, it is advantageous to administer the cells locoregionally to improve delivery to the sites of disease. A clinical trial of clustered regularly interspaced short palindromic repeats (CRISPR) gene-edited NK-cell therapy in glioblastoma is looking at the administration of therapy directly into a tumor (NCT04991870), and

clinical trials being conducted at MD Anderson are looking at the administration of CAR NK-cell therapy intraperitoneally to treat ovarian and pancreatic cancer (NCT05922930).

H&O What have clinical trials shown so far?

KR In the dose-escalation portion of our phase 1/2 study, we demonstrated the safety and efficacy of anti-CD19 CAR NK cells derived from umbilical cord blood in the setting of relapsed or refractory CD19-positive cancers, including non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). The results were very encouraging; those from the first 11 patients showed an overall response rate of 73% and a complete response rate of 64%.[1] The infused CAR NK cells expanded and persisted at low levels for at least 12 months. However, several patients in this early cohort subsequently underwent consolidative stem cell transplant following their response, so it was difficult to determine the extent to which the durability of the responses could be attributed to CAR NK-cell therapy alone.

In our subsequent expansion study, we evaluated CAR NK cells in a full cohort of 37 patients without routine consolidation, to allow a clearer assessment of the durability of the responses. In the final results, the complete response rate was 38% at 1 year of follow-up.[2] Response rates varied by disease subtype: 100% for patients who had low-grade NHL, 67% for patients who had CLL without transformation, and 41% for patients who had diffuse large B-cell lymphoma. The 1-year overall survival rate was 68%, and the 1-year progression-free survival rate was 32%.

CAR NK cells were not associated with the development of CRS, ICANS, or graft-versus-host disease. The treatment did not lead to an increase in the levels of inflammatory cytokines, including interleukin 6 (IL-6).

H&O Your study went from 11 to 37 patients over 4 years; were you hoping to enroll more than an additional 26 patients during that period?

KR We always hope to be able to recruit as many eligible patients as possible when we conduct a study like this one. However, during our study, several CD19-targeting CAR T-cell therapies received approval. This understandably affected enrollment because many patients were able to receive an approved therapy rather than participate in a clinical trial.

H&O What other research has looked at the use of CAR NK-cell therapy?

KR A phase 1 trial evaluated the use of a CD19-targeting CAR NK-cell product derived from induced pluripotent stem cells, FT596 from Fate Therapeutics, in 86 patients who had relapsed or refractory B-cell lymphoma.[3] The study took place across 9 centers in the United States. The researchers found that FT596 was well tolerated both as monotherapy and in combination with rituximab, and it induced deep and durable responses. CRS occurred in 1 of 18 patients (6%) who did not receive rituximab and in 9 of 68 patients (13%) who did receive rituximab. No neurotoxicity was seen. The results were similar to ours in terms of both safety and efficacy, confirming that NK cells have significant potential as a platform for cancer immunotherapy.

> We have the tools available to engineer NK cells to make them more potent and to redirect their specificity against one or multiple antigens.

H&O What other research on NK-cell therapy has your group conducted?

KR In another approach that we have investigated, rather than engineer the NK cells to express a CAR, we combine the cells with a bispecific engager, AFM13, designed to bind CD16 on NK cells and CD30 on tumor cells. This approach effectively redirects NK cells to target CD30-expressing malignancies. The phase 1/2 study enrolled 42 patients with Hodgkin lymphoma who had previously received a median of 7 lines of treatment, including checkpoint inhibitors and CD30-targeting monoclonal antibodies.[4] We saw an overall response rate above 90%, including a complete remission rate of approximately 67%.

H&O What side effects have been seen with CAR NK-cell therapy?

KR Just as with CAR T-cell therapy, lymphodepletion chemotherapy must be administered before the cells are infused. As a result, we see side effects related to hematologic toxicities; these are nearly always reversible and very easily managed. We have not seen any cases of CRS higher than grade 2, ICANS, or graft-versus-host disease.

Another benefit of CAR NK-cell therapy is that it can be given on an outpatient basis in most cases, whereas CAR T-cell therapy is more frequently given on an inpatient basis. The study of FT596 did not report any untoward or severe toxicities. The safety profile of these agents is very attractive.

H&O How can CAR NK-cell therapy be improved?

KR We have the tools available to engineer NK cells to make them more potent and to redirect their specificity against one or multiple antigens. For example, a disadvantage of NK cells is that their lifespan is much shorter than that of T cells—just 1 to 2 weeks in the absence of cytokine support. To overcome this problem, we can engineer NK cells to secrete a cytokine such IL-15 or IL-21, improving their in vivo persistence and antitumor activity. In fact, we recently demonstrated the benefit of IL-21–armored NK cells in glioblastoma.[5] We are also applying CRISPR gene editing to engineer NK cells to protect them from the immunosuppressive agents in the tumor microenvironment, such as transforming growth factor beta. Importantly, these CRISPR-edited NK cells are not just a preclinical concept—they are already being evaluated in early-phase clinical trials (NCT04991870). As we continue to deepen our understanding of NK-cell biology, the tumor microenvironment, and mechanisms of cancer resistance, we can take that new knowledge back to the bench and engineer NK cells that are more potent and more effective while still maintaining their safety profile. We can keep pushing the boundaries of what cell therapies can achieve.

MD Anderson established the Institute for Cell Therapy Discovery & Innovation in November 2024, with a focus on expanding the use of cell therapies across a broad range of malignancies including both hematologic cancers and solid tumors. Although our main emphasis is on cancer, we are also exploring strategies for the treatment of autoimmune diseases and infectious diseases.

A major area of active investigation is the development of engineered NK-cell therapies for solid tumors, in which the results have been more modest than those seen in the setting of hematologic malignancies. To address this problem, we are pursuing multi-antigen targeting, including dual-CAR engineering, or NK cells in combination with antibodies, such as the approach that I mentioned with AFM13. We are also looking at other combinatorial strategies in an effort to make the tumor microenvironment more receptive to trafficking and penetrance by NK cells.

Numerous clinical trials are ongoing at MD Anderson in different disease settings. We have 12 investigational new drugs that are being studied in early-phase clinical trials in both hematologic malignancies and solid tumors. We have also started a clinical trial in the setting of autoimmunity. We are committed to improving the accessibility of these therapies, especially because we can manufacture CAR NK cells much less expensively than CAR T-cell therapies. We hope the lower cost will allow us to expand access to treatment to many more patients worldwide, for whom these kinds of potentially lifesaving therapies are currently unavailable.

Disclosures

Dr Rezvani and The University of Texas MD Anderson Cancer Center have an institutional financial conflict of interest with Takeda Pharmaceutical and Affimed GmbH. Dr Rezvani participates on the Scientific Advisory Boards of Avenge Bio, Virogin Biotech, NAVAN Technologies, Caribou Biosciences, Bit Bio Limited, Replay Holdings, oNKo-innate, Alliance for Cancer Gene Therapy, Innate Pharma, and Shinobi Therapeutics. Dr Rezvani is the scientific founder of Syena.

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