ADVANCES IN LLM

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

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Chimeric Antigen Receptor Natural Killer Cells for the Treatment of Patients With B-Cell Malignancies

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H&O What are the outcomes associated with chimeric antigen receptor (CAR) T-cell therapy in patients with non-Hodgkin lymphoma (NHL) or chronic lymphocytic leukemia (CLL)?

KR For patients with NHL, the 1-year progression-free survival with axicabtagene ciloleucel (Yescarta, Kite) is approximately 45%. CAR T-cell therapy is not yet approved for the treatment of CLL. Clinical trials have shown that the rate of 1-year progression-free survival is approximately 30%.

H&O What prompted your study of cord blood–derived CAR natural killer (NK) cell therapy targeting CD19?

KR The data for CAR CD19 T-cell therapy in lymphoid malignancies were exciting. My colleagues and I decided to build on these results by engineering another subset of immune cells. We selected NK cells, mainly because these cells, unlike T cells, do not cause graft-vs-host disease. Graft-vs-host disease is a potentially lethal complication driven by T cells that occurs after allogeneic stem cell transplant. Another advantage is that CAR NK cells are suitable for allogeneic use. With commercial CAR T cells, the product is generated from the patient's own T cells and can be used to treat that patient only. CAR NK-cell therapy would not have to be patient-specific. Multiple doses of CAR NK cells could be manufactured from a single donor. The ability to use a product from one donor to treat multiple patients would reduce costs and increase accessibility to a larger population. Our trial showed that CAR NK cells have less toxicity than CAR T cells.

H&O What was the design and outcome of your study?

KR My colleagues and I conducted a phase 1/2, dose-escalation trial of CAR NK cells in patients with relapsed or refractory CD19-positive cancers (NHL or CLL). The phase 1 portion has been completed, and we have moved onto the phase 2 portion. The trial tested 3 dose levels: 1×10^5 CAR NK cells/kg, 1×10^6 CAR NK/kg, and 1×10^7 CAR NK cells/kg. Patients received a single infusion of CAR NK cells after lymphodepleting chemotherapy. We reported data from the dose-escalation portion of the study in the *New England Journal of Medicine*.

We treated 11 patients with relapsed or refractory B-cell malignancies; 5 had CLL and 6 had NHL. The population was very refractory, and patients had previously received up to 11 lines of therapy. The patients' median age was 60 years. We did not observe complications related to cytokine release syndrome, neurotoxicity, or any other toxicity typically associated with a CAR

T-cell product. No patients developed graft-vs-host disease. The complications we observed were mainly related to the conditioning chemotherapy, and included nausea, vomiting, and diarrhea. We also observed a transient and fully reversible drop in blood counts, likely related to the conditioning chemotherapy. (Although the possibility that CAR NK cells contributed to the cytopenia cannot be excluded.)

Among the 11 patients treated, 8 achieved a response. Seven of the responses were complete remissions. We documented in vivo expansion and persistence of the CAR NK cells for up to 12 months after the infusion.

H&O Were there any other observations of interest?

KR We were encouraged by the efficacy data. The toxicity profile was also promising, particularly in comparison to other cell therapies, including CAR T-cell therapy. Other types of CAR T-cell therapies are associated with severe toxicities that can require hospitalization or even admission to an intensive care unit. In our study, no patients required admission to an intensive care unit to treat toxicities. Based on these encouraging safety data, we are now offering treatment with NK CAR cells as an outpatient procedure.

Another important observation was the persistence of the cells. Donors and recipients were human leukocyte antigen (HLA)-mismatched. The expectation was that once the patient's T cells recovered after lymphodepleting chemotherapy, the mismatched CAR NK cells would be rejected. However, the cells persisted for a year or even longer after infusion, suggesting that a degree of tolerance was established between the donor CAR NK cells and the recipient. My colleagues and I are now performing several studies to try and understand the mechanism behind the tolerance that is being induced.

H&O What is the process of manufacturing CAR NK cells?

KR Our research evaluated umbilical cord blood, but there are other sources of NK cells. We are fortunate to have a cord bank at MD Anderson Cancer Center. We obtain a frozen cord from the cord bank. We thaw the cells and isolate the NK cells. In the Good Manufacturing Practice (GMP) facility at MD Anderson, we introduce the CAR using a virus. It is a retroviral vector expressing genes that encode anti-CD19 CAR, interleukin 15, and inducible caspase 9 (as a safety switch). This CAR allows the NK cells to recognize the CD19 antigen on the surface of the cancer cells.

The entire process from the time that we isolate the NK cells from the frozen cord unit to the infusion of the CAR NK cells into the patient takes approximately 2 weeks. These cells are grown and expanded in our GMP facility.

The administration of CAR NK-cell therapy begins with conditioning chemotherapy consisting of 3 days of fludarabine and cyclophosphamide, the same regimen given with CAR T-cell therapy. Two days afterward, the patient receives an intravenous infusion of NK cells, similar to a blood transfusion. We then wait for the cells to do their job.

> The ability to use a product from one donor to treat multiple patients would reduce costs and increase accessibility to a larger population.

H&O What are the advantages of using CAR T cells vs CAR NK cells?

KR As I mentioned earlier, NK cells do not cause graft-vs-host disease, which is a devastating condition caused by donor T cells that attack healthy cells in the recipient. Because NK cells do not cause graft-vs-host disease, there is no need for matching between the donor and the recipient. Another important advantage is the ability to make multiple doses of CAR NK cells from one donor to treat many patients. In our laboratory, we have shown that it is possible to manufacture hundreds of doses of CAR NK cells from one single unit of cord blood. Having said that, in our recent study, we used one donor for one patient. Our trial was first-in-human, and therefore the US Food and Drug Administration (FDA) required that we stagger the patients with at least a 2-week gap between enrollments. Because the product was fresh and not cryopreserved, we could not treat multiple patients with CAR NK cells manufactured from one cord.

Ultimately, our plan is to expand and freeze the CAR NK cells and then store them in a cell biobank. When a patient comes to the clinic, we will retrieve the CAR NK cells off the shelf from the bank, thaw them, and then infuse them. CAR NK-cell therapy has the potential to be literally an off-the-shelf product that can significantly reduce the time from diagnosis to treatment.

H&O Are there types of patients who would benefit from CAR NK cells vs CAR T cells?

KR CAR NK cells target the cancer in a similar manner to CAR T cells. The initial results from our study are encouraging, but we need to treat more patients with longer follow-up. One possibility is that CAR NK cells may be advantageous in older, frail patients based on the improved safety profile. CAR NK cells may also be beneficial in patients with rapidly advancing disease or patients who have received many courses of chemotherapy that caused lymphopenia. In patients with lymphopenia, collection of the leukapheresis product for the manufacture of CAR T cells is more challenging. The CAR NK-cell product is generated from a healthy donor and is waiting on a shelf.

H&O What are your plans for continued evaluation of CAR NK cell therapy?

KR Our efforts are twofold. In collaboration with Takeda Pharmaceuticals, we are developing a multicenter study with the objective of obtaining approval from the FDA for our CAR 19 product. We are also working in the laboratory to develop CAR NK cells that target solid tumors, such as glioblastoma. Our research targeting CD19 with CAR 19 NK cells was to establish proof of principle. Now that we have shown safety and potential efficacy, we would like to expand this strategy to treat other types of cancer.

We are continuously striving to innovate. We have developed CARs against multiple types of cancers, and are currently in the process of testing and preclinical validation. We hope to be able to bring these treatments to the clinic as soon as possible.

Disclosure

Dr Rezvani has license and research agreements with Takeda to develop CB-CAR NK cells for the treatment of B-cell malignancies and other cancers. She has received educational grants from Affimed and Pharmacyclics. She is a member of the scientific advisory boards of Virogen, Adicet Bio, and GEMoaB.

Suggested Readings

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