Medicine, Drug development

Novel CAR T cells and cord blood-derived CAR NK cells for relapsed acute myeloid leukemia after allogeneic hematopoietic stem cell transplantation

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Researchmap https://researchmap.jp/hnaoki/?lang=en

Abstract

Many AML patients cannot be cured by chemotherapy alone and undergo allogeneic hematopoietic stem cell transplantation, but a significant number still die from relapse. CAR T-cell therapy involves genetically modifying a patient's own T cells to attack cancer cells and is used to treat conditions like leukemia and malignant lymphoma. While its development for AML is anticipated, the current reality is that no suitable target antigens have been identified. We identified the KG2032 antibody from our library of 14,000 anti-AML cell antibodies. This antibody recognizes approximately half of the diverse HLA-DRB1 types. CAR T or NK cells derived from the KG2032 enables these cells to attack only the leukemia cells without attacking the normal blood cells of AML patients who have relapsed after allogeneic transplantation. We generated KG2032-derived CAR T cells and umbilical cord blood-derived CAR NK cells, both of which demonstrated remarkable antitumor effects.

Background & Results

Many AML patients cannot be cured by chemotherapy alone, necessitating allogeneic hematopoietic stem cell transplantation. However, recurrence-related mortality remains high, highlighting the need for new treatments for AML patients after allogeneic transplantation. While CAR T cells have demonstrated remarkable efficacy in other blood cancers, their development for AML faces challenges due to the lack of suitable target antigens capable of distinguishing AML cells from normal hematopoietic cells. Furthermore, CAR T-cells must be manufactured for each individual patient, a process that is time-consuming and costly, making the development of allogeneic cell therapies highly desirable. We initiated our research by creating multiple monoclonal antibodies that bind to AML cells to search for new target antigens. We identified an antibody named KG2032 as an AML-specific antibody from approximately 14,000 monoclonal antibody clones that bind to AML cells. This antibody strongly binds to AML cells derived from the bone marrow of AML patients but does not bind to healthy human peripheral blood cells other than B cells. Furthermore, we determined that the protein bound by KG2032 is HLA-DRB1. HLA-DRB1 is like a blood type for white blood cells, varying between individuals. We found KG2032 binds to approximately half of the HLA-DRB1 types.

Allogeneic hematopoietic cell transplantation is performed in many AML patients. The HLA-DRB1 types of the patient and donor frequenlty differ. If KG2032 binds to the HLA-DRB1 on the patient's AML cells but not on the donor's, KG2032 specifically recognizes only the AML cells. CAR T cells engineered with the KG2032 antibody demonstrated remarkable antitumor activity. Furthermore, using the KG2032-derived CAR, we developed umbilical cord blood-derived CAR NK cells that exhibited significant antitumor effects against AML cells.

Significance of the research and Future perspective

This research finding holds the potential to save some AML patients who could not previously be saved even with allogeneic hematopoietic cell transplantation. Furthermore, if CAR NK cells derived from umbilical cord blood become clinically available, they could enable readily accessible, more affordable gene and cell therapies.

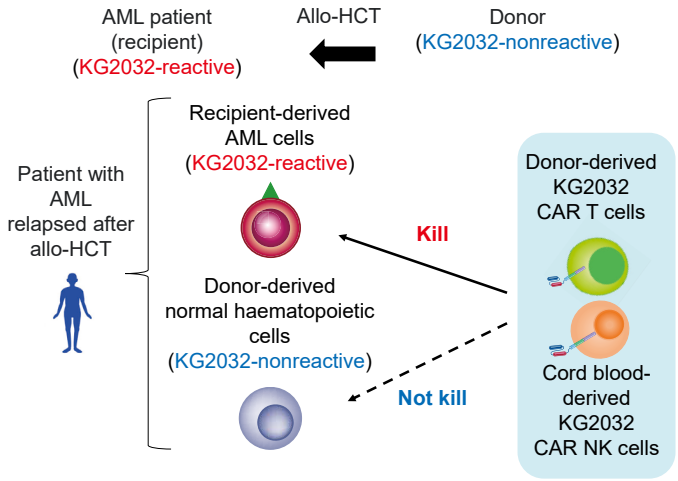

Fig. 1 Novel CAR T cells and cord blood-derived CAR NK cells for relapsed acute myeloid leukemia after allogeneic hematopoietic stem cell transplantation.
When a patient with KG2032-reactive AML undergoes allogeneic hematopoietic stem cell transplantation from a KG2032-unreactive donor, administration of donor T cells or cord blood-derived NK cells transduced with the KG2032-derived CAR will target the patient's AML cells but not the donor-derived normal hematopoietic cells.

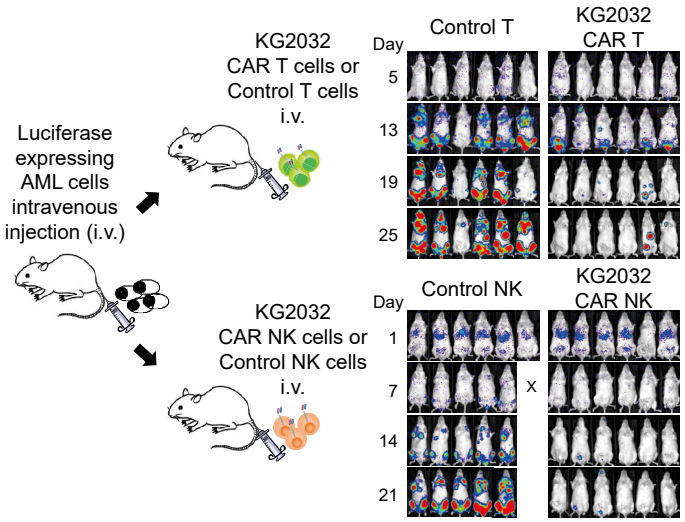

Fig. 2 Significant anti-tumor effects of KG2032 CAR T/NK cells
Fluorescence intensity reflects leukemia burden. In the control cell administration group, leukemia progressed over time, but in the KG2032 CAR T/NK cell administration group, leukemia progression was significantly suppressed.

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Treatise Ikeda, Shunya et al. CAR T or NK cells targeting mismatched HLA-DR molecules in acute myeloid leukemia after allogeneic hematopoietic stem cell transplant. Nat Cancer. 2025, 6, 595–611. doi: 10.1038/s43018-025-00934-1

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Keyword CAR T cell, CAR NK cell, leukemia