Autologous T Cells Modified to Co-express CD33-Specific Chimeric Antigen Receptor and a Kill Switch for Treatment of CD33+ Acute Myeloid Leukemia

Degang Song, Ph.D. 1, Michael H. Swartz 2, Linhua Tian 1, Fernando Carvajal-Borda 1, Jacques Plummer 1, Rutul R. Shah 1, William G. Wierda, M.D., Ph.D. 3, Laurence J. N. Cooper, M.D., Ph.D. 4, Tim Chan, Ph.D. 5

1 Intrexon Corporation, Germantown MD; 2 Formerly at Intrexon Corporation, Germantown, MD; 3 Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; 4 ZIOPHARM Oncology, Boston, MA

Abstract

Relapsed/refractory acute myeloid leukemia (AML) is an aggressive malignancy with poor outcomes underlining the need to implement new therapies. Adoptive transfer of genetically modified T cells with specificity redirected through a chimeric antigen receptor (CAR) has emerged as a promising strategy, particularly for Blastic plasmacytoid dendritic cell neoplasm (BPDCN). As CD33 is a cell surface antigen targeted for antibody-dependent cellular cytotoxicity (ADCC), this therapy is also approved for BPDCN. However, there is a high incidence of relapse in patients with AML, suggesting a need to implement new therapies. Here, we describe generation of CD33-specific CAR-T cells expressing a cytokine and a kill switch facilitating in vivo persistence and secretion of cytokines and cytokine release.

Specific in vitro Cytotoxicity and Cytokine Induction by CD33-CAR-T cells

Background

- Patients with AML often face treatment failures and high relapse rates. The overall survival following relapse is poor.
- Limited treatment options are currently available for patients with relapsed/refractory AML.
- CD33 is a transmembrane glycoprotein commonly expressed on AML blast cells but also expressed on normal myeloid cells and on activated T and NK cells.
- CD33 is an attractive target for immunotherapy.

Co-expression of CD33-specific CAR and Kill Switch in T cells

CD33-CAR-T Cells Increased Killing and Cytokine Induction by CD33-CAR-T cells

In vitro Assessment of CD33-CAR-T cells From a Donor with AML

Summary

- CD33-specific CAR and kill switch were co-expressed in T cells using a lentiviral vector.
- CD33-CAR-T cells exhibited redirected specificity for CD33 in vitro as evident by cytokine release and cytotoxicity in response to CD33+ target cells.
- HER1t expressing CD33-CAR-T cells were conditionally eliminated by cetuximab-mediated ADC both in vitro and in vivo.
- CD33-CAR-T cells elicited cytokine response, persisted in mice and eliminated AML tumor that significantly improved survival.
- A Phase 1 clinical trial for treatment of relapsed/refractory AML has been initiated at MD Anderson Cancer Center (NCT03126864).

Conflicts of Interest:

No conflicts of interest.

Disclosures:

No disclosures.

Figure captions:

1. Expression of CD33-specific CAR and IL-15 specific T cells for lentiviral transduction. (A) Human CD33+ AML cells were transduced with CD33 specific CAR-transduced lentivector and infected with LV-CAR-T cells expressing IL-2, IL-15, IL-18, TNF-α, IFN-γ and GM-CSF. (B) Exhausted CAR+ T cells were transduced with LV-CAR-T cells expressing IL-2, IL-15, IL-18, TNF-α, IFN-γ and GM-CSF. (C) Human CD33+ AML cells were transduced with CD33 specific CAR-transduced lentivector and infected with LV-CAR-T cells expressing IL-2, IL-15, IL-18, TNF-α, IFN-γ and GM-CSF. (D) Exhausted CAR+ T cells were transduced with LV-CAR-T cells expressing IL-2, IL-15, IL-18, TNF-α, IFN-γ and GM-CSF.

2. Cytokine production of CD33-CAR-T cells expressing HER1t. (A) In vitro, phycoerythrin (PE) labeled CD33 specific CAR-transduced lentivector infected T cells were incubated with or without cetuximab (2 μg/mL) and cultured in medium with IL-2 and IL-15. (B) Cytokine production of CD33-CAR-T cells expressing HER1t. (C) Cytokine production of CD33-CAR-T cells expressing HER1t and Δζ. (D) Cytokine production of CD33-CAR-T cells expressing HER1t and Δζ and Δζ-2 cytokines.

3. In vivo efficacy of CD33-CAR-T cells in AML tumor model. (A) Nude mice were transplanted subcutaneously with 1.5 × 106 MOLM-13 or EL4 cells. (B) Mice were randomized into saline (CD33-CD19neg) tumor. A single administration of human CD33-CAR-T cells resulted in a significant reduction in tumor burden and improvement in overall survival with an overall survival rate of 96% compared to 5% for control treated mice. (C) Tumor burden was determined in immunocompromised (NSG) mice bearing MOLM-13 tumor cells. A single administration of human CD33-CAR-T cells resulted in a significant reduction in tumor burden and improvement in overall survival with an overall survival rate of 96% compared to 5% for control treated mice. (D) Tumor burden was determined in immunocompromised (NSG) mice bearing MOLM-13 tumor cells. A single administration of human CD33-CAR-T cells resulted in a significant reduction in tumor burden and improvement in overall survival with an overall survival rate of 96% compared to 5% for control treated mice. (E) Tumor burden was determined in immunocompromised (NSG) mice bearing MOLM-13 tumor cells. A single administration of human CD33-CAR-T cells resulted in a significant reduction in tumor burden and improvement in overall survival with an overall survival rate of 96% compared to 5% for control treated mice. (F) Tumor burden was determined in immunocompromised (NSG) mice bearing MOLM-13 tumor cells. A single administration of human CD33-CAR-T cells resulted in a significant reduction in tumor burden and improvement in overall survival with an overall survival rate of 96% compared to 5% for control treated mice.