Effects of NKTR-255, a polymer conjugated human IL-15, on efficacy of CAR T cell immunotherapy in a preclinical lymphoma model

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Background

Immunotherapy with CD19 CAR T cells achieves complete or partial remission in a fraction of patients with B cell malignancies, but disease progression remains common. IL-15 promotes T-cell proliferation and survival, and may enhance CAR T cell efficacy. However, exploiting native IL-15 is challenging due to its unfavorable pharmacokinetics and tolerability. In contrast, NKTR-255 is a polymer-conjugated IL-15 that retains binding affinity to IL-15Rα, maintaining full spectrum of IL-15 biology. NKTR-255 also exhibits improved pharmacokinetics thereby providing sustained pharmacodynamic responses without the need for daily dosing. We investigated the effects of NKTR-255 on human CD19 CAR T cells both in vitro and in an in vivo xenograft B-cell lymphoma model.

Methods

T cells expressing a CD19/4-1BB/CD3ζ CAR were generated from healthy donors. Briefly, CD4 and CD8 T cells were isolated and transduced separately with CD19 CAR lentiviral vector (Fig. 1), transduced cells were sorted then expanded with LCL (lymphoblastoid B-cell line) cells for 14-16 days. For in vitro studies, CAR T cells were incubated with NKTR-255. STAT5 phosphorylation and CFSE dilution were assessed by flow cytometry. For in vivo studies, NSG mice received 5x10⁵ Raji lymphoma cells iv on day (D)-7 and a subtherapeutic dose (0.8x10⁶) of CAR T cells on D0 and weekly injections of NKTR-255 (0.3mg/kg) starting on D7. Mice were euthanized on D11, 14, 21 and 28 post CAR T cell infusion. Single cell suspensions were made from bone marrow and CAR T cells, Ki67, PD1 and TIM3 expression were assessed by flow cytometry. Graphs show mean ± SEM.

Results

Figure 3: NKTR-255 treatment at 0.1 mg/kg and 0.3 mg/kg in combination with CAR T cells leads to decreased tumor burden and eradication of Raji lymphoma in NSG mice compared to CAR T cells alone. (A) Raji-bearing NSG mice received a subtherapeutic dose of CAR T cells on D0 followed by 0.3, 0.1 or 0.3 mg/kg of NKTR-255 starting on D6 than weekly. Mice were imaged weekly and tumor bioluminescence images for representative timepoints are shown in (B) and average radiance in (C). Survival is shown in (D).

Figure 4: NKTR-255 in combination with CAR T cells results in increased CAR T cells in the blood, decreased tumor burden and increased survival of Raji lymphoma bearing NSG mice. (A) Raji-bearing NSG mice received CAR T cell infusions on D0 followed by 0.3mg/kg of NKTR-255 starting on D-1, D7 or D14 than weekly (5 mice/group). (B) Mice were bled weekly and CD8 and CD4 CAR T cells were identified by flow cytometry. Tumor burden was assessed by weekly bioluminescence imaging shown in (C) and survival in (D).

Conclusions

• CD8 and CD4 CAR T cells express IL-15-Rα and NKTR-255 induces STAT5 phosphorylation and proliferation in a dose-dependent manner.
• NKTR-255 in combination with CAR T cells decreases tumor burden and increases survival of NSG mice in a Raji lymphoma model compared to CAR T cells alone.
• NKTR-255 treatment resulted in increased accumulation and proliferation of CAR T cells in the bone marrow of Raji bearing NSG mice and decreased prolonged dual expression of PD1 and TIM3.
• Tumor-bearing mice previously treated with NKTR-255 and CAR T cells are able to reject tumor rechallenge supporting CAR T cell persistence.
• NKTR-255 administration improves the antitumor efficacy and kinetics of CD19 CAR T cells, supporting development of clinical trials of combination therapy with NKTR-255 and approved CD19 CAR T cell products.

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