NKTR-255, a polymer-conjugated IL-15 enhances anti-tumor NK cell responses and synergizes with monoclonal antibodies to provide long-term survival in human lymphoma models

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Background

IL-15 is a cytokine that activates and provides survival benefit to NK cells. Exploring the therapeutic value of native IL-15 has been challenging due to its unordered pharmacokinetic properties and toxicity. NKTR-255 is a polymer-conjugated human IL-15 that retains binding affinity to the alpha subunit of IL-2 receptor and exhibits reduced clearance to provide a sustained pharmacodynamic response. NKTR-255 has potential for providing an enhanced immunotherapeutic effect when combined with monoclonal antibodies that target tumor cells, as antibodies can potentially enhance the biological activity of IL-15 (IL-15CC). Here we summarize the preclinical proof-of-principle data of NKTR-255 on NK cells, NK cell ADCC mechanisms, and in combination with therapeutic antibodies to provide an enhanced immunotherapeutic effect in pre-clinical lymphoma models.

Methods

Results

In vivo studies demonstrated that NKTR-255 dose-dependently induced phosphorylation of STAT5 and increased proliferation of NK cells in the bone marrow, which correlated with significantly increased NK cell numbers in bone marrow, but robustly enhanced their Granzyme B, CD16 expression and ADCC mechanism in a NKTR-255 dose-dependent manner. Furthermore, NKTR-255 (0.3 mg/kg) treatment not only synergized with daratumumab (anti-CD38 Ab) or rituximab (anti-CD20 Ab), synergistically provided long-term survival in the Daudi B-cell lymphoma model, NKTR-255 combined with a tumor-directed antibody, either daratumumab or rituximab, synergistically enhanced proliferation, CD69 and CD107a expression and Granzyme B protein in KHYG-1 cells (EC50 values for pSTAT5: 0.2 ng/ml, proliferation: 5 ng/ml) and human primary NK cells. The combination of NKTR-255 with daratumumab or rituximab significantly increased mean tumor cell depletion in a single dose experiment (vs untreated, Mean tumor cell depletion: NKTR-255 0.03 mg/kg: 75%, NKTR-255 0.3 mg/kg: 97%, Daratumumab: 80% vs untreated, 25%). In the Daudi B-cell lymphoma model, NKTR-255 combined with a tumor-directed antibody either daratumumab or rituximab synergistically increased both in vitro and in vivo tumor cell depletion in the bone marrow. NKTR-255 has potential to be broadly applied with the tumor-directed antibodies that trigger ADCC to enhance their therapeutic efficacies.

Conclusions

- NKTR-255 dose-dependently induces pSTAT5 and proliferation in human NK cells.
- NKTR-255 and CD15 cross-linking synergistically enhances NK cell proliferation and activation.
- The properties of NKTR-255 to boost NK proliferation and activation with CD15 cross-linking translates into enhanced in vivo ADCC activity.
- NKTR-255 has a potential to be broadly applied with the tumor-directed antibodies that trigger ADCC to enhance their therapeutic efficacies.
- In the bone marrow, an optimal growth environment for hematologic malignancies, NKTR-255 combination treatment enables effective ADCC mechanism-mediated tumor killing by simultaneously increasing NK cell numbers and their activity.

References


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Figure 1. NKTR-255 showed a dose-dependent phosphorylation of STAT5 and increased proliferation in the human NK cell line, KHYG-1. (A) KHYG-1 were stimulated with the indicated concentration of NKTR-255 for 10 minutes and the induction of pSTAT5 was measured using the pSTAT5/Dox64 mCherry reporter following 4 hours culture was assessed by acquisition of anisotropy in the top hemisphere using Cell-Id 2 (v 2.0.9).

Figure 2. NKTR-255 showed a dose-dependent phosphorylation of STAT5 and increased proliferation in human NK cells. Human primary NK cells were cultured overnight with or without 1 µg/ml NKTR-255. The NK cells (effector cells) were labeled with fluorochrome-conjugated antibodies against CD56 and CD16 and were conjugated with IgG-coated plates. CD69 (A) and CD107a (B) expression on NK cells were assessed by flow cytometry. Secreted Granzyme B protein (C) was measured from culture supernatant by ELISA.

Figure 3. NKTR-255 and CD15 cross-linking synergistically enhanced NK cell proliferation. KHYG-1-derived human NK cells were cultured with 100 ng/ml NKTR-255 or non-coated or 0.1 mg/ml human IL-15-coated plates for 5 days. NK cell proliferation following the culture was assessed by flow cytometry.

Figure 4. NKTR-255 and CD15 cross-linking synergistically enhanced NK cell activation. Human PBMCs were cultured overnight with 100 ng/ml NKTR-255 on non-coated or 0.1 mg/ml human IL-15-coated plates. CD15 and CD15a expression on NK cells were assessed by flow cytometry. Secreted Granzyme B protein was measured from culture supernatant using ELISA.

Figure 5. NKTR-255 enhanced daratumumab-mediated ADCC to multiple myeloma cell line, RPMI-8226.

Figure 6. NKTR-255 enhanced daratumumab-mediated ADCC to multiple myeloma cell line, RPMI-8226.

Figure 7. NKTR-255 expanded and activated NK cells in the bone marrow compartment.

Figure 8. NKTR-255 and daratumumab synergized to deplete bone marrow resident tumor cells.

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