NKTR-214 in combination with radiation therapy produces a potent in situ vaccine for B78 melanoma.

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BACKGROUND

Purpose: We wanted to investigate the prospect of using NKTR-214 (an engineered IL2 agonist) as a replacement for IL2 in our current in situ vaccine treatment regimen.

Targeted immunotherapies, in combination with radiation therapy, are effective anti-cancer immunotherapy regimens: We have helped develop the use of a tumor-specific immunoconjugate (IC) to treat different forms of cancer. An IC is a monoclonal antibody (mAb) specific for a tumor surface antigen with two IL2 molecules attached to the constant region of the antibody. This combination leads to a tumor targeted innate immune response and concentration of IL2 at the tumor microenvironment. Radiation therapy (RT) is a tumor-targeted treatment that can be used to enhance immunotherapy, through its ability to increase the release of local pro-inflammatory cytokines, cause immunogenic cell death, and increase neo-antigen exposure on MHC-I molecules resulting in a more diverse T-cell receptor repertoire. RT alone rarely generates an effective in situ vaccine effect, as, in part, a poor persistence of activated tumor-specific lymphocytes. We have found that by combining RT with intratumoral (IT) injections of tumor-targeted immunotherapy we can create an enhanced immune response capable of eradicating tumors. Preclinical data have shown that one dose of local RT combined with five injections of intratumoral IC (IT IC), starting five days after RT, can work synergistically to cause tumor regression and disease-free animals in a single syngeneic melanoma tumor model. Not only are most mice receiving RT+IT IC cured of their tumor burden, but they also exhibit immunologic memory that is demonstrated by their ability to reject a second challenge with melanoma cells. This immunologic memory demonstrates we can create an in situ vaccine using RT+IT IC².

NKTR-214 circumvents the limitations of IL-2: Using IL2 in a treatment regimen does come with consequences, however. It has a short half-life in vivo and patients must be infused continuously with the cytokine in order to achieve a therapeutic dose. IL2 can activate anti-tumor immune cells (i.e. NK cells, CD4+, CD8+ T cells). Immune inhibitory T regulatory (Treg) cells, which are present in the tumor microenvironment and used by tumors to evade an immune response, are also activated by IL2. Finally, IL2 has dose limiting toxicity that can be fatal. Nektar Therapeutics has circumvented these IL2 limitations with NKTR-214 by attaching 6 polyethylene glycol (PEG) molecules to the IL2 molecule. The location of the PEG molecules results in receptor bias against the IL2Rα portion of the IL2 receptor and towards the IL2Rβγ portion of the receptor. This bias allows NKTR-214 to better activate anti-tumor immune cells like NK cells, CD4+ T cells, and CD8+ T cells, while not activating immune inhibitory Treg cells. This leads to increased CD8/Treg ratios in human and murine tumors. Furthermore, the PEGylation makes NKTR-214 a drug that becomes more active as PEG molecules fall off in vivo, which increases the half-life and maximum tolerated dose of the drug.

RESULTS

A.

IV NKTR-214 is Synergistic with Radiation to Cause Significant B78 Melanoma Tumor Regression and Disease Free Mice

B.

IV NKTR-214 in Combination with Radiation Causes Greater B78 Melanoma Tumor Regression than IV IL2 with Radiation

C.

IV NKTR-214 in Combination with Radiation Causes Greater B78 Melanoma Tumor Regression than IT IL2 with Radiation

METHODS

Cell Culture

B78 cells were grown in culture with RPMI-1640 media supplemented with 10% FBS, 2mM glutamax, and 1% Pen/Strep. Cells were grown at 37°C in an environment of 5% CO2.

Tumor Inoculation, Drug Treatment, Tumor Monitoring

B78 cells were grown in culture with RPMI-1640 media supplemented with 10% FBS, 2mM glutamax, and 1% Pen/Strep. Cells were grown at 37°C in an environment of 5% CO2.

RESULTS (CONTINUED)

IV NKTR-214 in Combination with Radiation Results in Prolonged Survival Compared to IT IL2 in Combination with Radiation

E.

Comparing Complete Response and Percent B78 Rechallenge Rejection

CONCLUSIONS AND FUTURE DIRECTIONS

- RT alone and NKTR-214 alone slow tumor growth but do not, on average, result in tumor regression and disease-free animals
- IV NKTR-214 in combination with 12 Gy RT results in a stronger anti-tumor response than IV or IT IL2 in combination with 12 Gy RT
- The immunologic memory achieved with RT + IV NKTR-214 is more robust than the immunologic memory achieved with RT + IT IL2
- We hope to show, via flow cytometry, that an increase in CD8:Treg ratio is seen at the tumor when NKTR-214 is used with RT
- Immune depletion studies are currently ongoing
- Further evaluation of RT + NKTR-214 + K322A (a tumor specific antibody) is required before a conclusion can be drawn about the ability of a tumor specific mAb to synergize with RT + NKTR-214

REFERENCES AND ACKNOWLEDGMENTS


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