Ikeda et al. Journal for ImmunoTherapy of Cancer 2014, 2(Suppl 3):P20
http://www.immunotherapyofcancer.org/content/2/S3/P20

Journal for ImmunoTherapy of Cancer

POSTER PRESENTATION Open Access

Tumor-specific donor lymphocyte infusion therapy with allogeneic T cells utilizing novel retrovirus vector silencing endogenous TCR expression

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From Society for Immunotherapy of Cancer 29th Annual Meeting
National Harbor, MD, USA. 6-9 November 2014

Background

Donor Lymphocyte infusion (DLI) is a therapy for the patients with relapsed hematological malignancy after allogeneic hematopoetic stem cell transplantation. However, the development of Graft-Versus-Host Disease (GVHD) is a serious adverse event and the efficacy is limited when one needs to control the GVHD. To inhibit the development of GVHD with increased tumor-specificity of transferred allogeneic lymphocytes, here we demonstrate the development of DLI with lymphocytes engineered to express tumor-specific T cell receptor (TCR) in combination with decreased GVHD-inducing potential utilizing the novel retrovirus vector (siTCR vector) that specifically silences endogenous TCR in gene-engineered T cells.

Methods

Human PBMC were transduced with a high affinity TCR specific to a cancer/testis antigen, NY-ESO-1, by the retrovirus vector with siRNA specific to the endogenous TCR. Resulting TCR gene-transduced T cells were examined for their reactivity to allogeneic LCL by ^{3}H uptake proliferation assay. Immunodeficient NOG mice were inoculated with a NY-ESO-1-expressing human melanoma cell line NW-MEL-38, received TCR gene-transduced T cells, and monitored for tumor growth and the development of GVHD.

Results

Human lymphocytes that were genetically engineered to express a high affinity NY-ESO-1-specific TCR with siTCR vector showed reduced expression of endogenous TCR associated with the dramatically diminished reactivity to allogeneic lymphocytes. When administrated into NOG mice, these TCR gene-transduced T cells induced tumor regression without the development of GVHD.

Conclusions

The results here suggest that the allogeneic T cells transduced with a tumor-specific TCR by siTCR vector showed diminished GVHD potential. These T cells will be applicable to the donor lymphocytes infusion therapy after allogeneic stem cell transplantation for the treatment of hematological malignancy, providing diminished GVHD and increased tumor eradication.

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Published: 6 November 2014

doi:10.1186/2051-1426-2-S3-P20
Cite this article as: Ikeda *et al.*: Tumor-specific donor lymphocyte infusion therapy with allogeneic T cells utilizing novel retrovirus vector silencing endogenous TCR expression. *Journal for ImmunoTherapy of Cancer* 2014 **2**(Suppl 3):P20.

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