Shiku et al. Journal for ImmunoTherapy of Cancer 2014, 2(Suppl 2):P45
http://www.immunotherapyofcancer.org/content/2/S2/P45

Journal for ImmunoTherapy of Cancer

POSTER PRESENTATION Open Access

P71. Adoptive transfer of TCR gene-transduced lymphocytes targeting MAGE-A4 for refractory esophageal cancer

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From 1st Immunotherapy of Cancer Conference (ITOC1)
Munich, Germany. 12-14 March 2014

Background

Engineering the antigen receptor gene in patients' lymphocytes is one promising strategy to create antigen-specific lymphocytes without senescent phenotypes. The strategy provides an opportunity to extend the application of adoptive T cell therapy for cancer patients. However, this concept has not been tested in the epithelial cancer patients.

Materials and methods

MAGE-A4-specific TCR α and β chains were cloned from a human T cell clone that recognises MAGE-$A4_{143-151}$ peptide in a HLA-A*24:02 restricted manner. This T cell clone did not show any cross reactivity to the peptides with homology to the MAGE-$A4_{143-151}$ epitope. A retroviral vector that encodes these TCR chains without any artificial modification was constructed; the lymphocytes transduced with the retroviral vector killed the MAGE-A4 expressing tumor in vitro and inhibited the tumour growth in the NOG immunodeficient mice.

A phase I clinical trial of TCR gene therapy targeting MAGE-A4 was performed to treat refractory esophageal cancer patients without lympho-depleting pre-conditioning. The trial was designed as a cell-dose escalation consisting of three cohorts, $2x10^8$, $1x10^9$ and $5x10^9$ cells/patient. Vaccines with the cognate peptide were also given following adoptive transfer of lymphocytes on day 14 and day 28.

Results

The treatment was tolerable with no adverse events associated with transferred cells or any viral toxicity. In all ten patients of the 3 cell-doses, the transferred lymphocytes were detected in their peripheral blood in a dose-dependent manner during the first 14 days. In 4 patients, the infused cells have been persisting more than 5 months after the transfer. The transferred lymphocytes that were harvested from the patients more than 50 days after the transfer were found to sustain the reactivity to the antigen-expressing tumour cells. Three patients showed SD or long tumour free status.

Conclusions

This approach may extend the availability of adoptive T cell therapy for epithelial cancer patients by providing tumour-reactive and long surviving lymphocytes.

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Published: 12 March 2014

doi:10.1186/2051-1426-2-S2-P45
Cite this article as: Shiku *et al.*: P71. Adoptive transfer of TCR gene-transduced lymphocytes targeting MAGE-A4 for refractory esophageal cancer. *Journal for ImmunoTherapy of Cancer* 2014 **2**(Suppl 2): P45.

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