Vaccination of patients with advanced non-small cell lung cancer with an optimized hTERT cryptic peptide (Vx-001)

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Abstract

Purpose: To evaluate the immunological and clinical efficacy of the optimized peptide TERT572Y (Vx-001) presented by HLA-A*0201 to patients with advanced non-small cell lung cancer (NSCLC).

Patients and methods: Twenty-two patients with residual (n=8) or progressive (n=14) advanced NSCLC following chemotherapy and/or radiotherapy received two subcutaneous injections of the optimized TERT572Y peptide followed by four injections of the native TERT572 peptide given every 3 weeks. Peptide-specific immune responses were monitored by Elispot assay and/or TERT572Y pentamer staining. Clinical outcome was compared with that of 22 case-matched historical control patients.

Results: Thirteen (59%) out of 22 patients completed the vaccination program. Adverse events (grade I) consisted primarily of local skin reactions. TERT572-specific CD8+ cell counts were 18 (76.2%) out of 22 patients after the 2nd vaccination and 10 (90.9%) out of 11 patients after the 6th vaccination. Stable disease occurred in 8 (36.4%) patients with a median duration of 11.2 months. Patients with immunological response (n=16) had a significantly longer time to disease progression and overall survival than non-responders (n=6); disease-free survival (p=0.046) and p=0.032, respectively. The estimated median overall survival was 30.0 months (range, 2.8-40.0) and 4.1 months (range, 2.4-10.2) for immunological responders and non-responders, respectively. Moreover, median overall survival was 20.6 months (60% CI 10.4-43.6) and 6.1 months (60% CI 4.4-7.8) for the vaccinated and case-matched historical control patients, respectively (p=0.074).

Conclusions: TERT572Y peptide vaccine is well tolerated and effective in eliciting a specific T-cell immunity which seems to be associated with prolonged patients’ survival.

Introduction

Antitumor immunotherapy is mainly based on the activation of specific T lymphocytes (CTLs) recognizing endogenously processed peptides derived from tumor antigens and presented at the cell surface in association with HLA class I molecules (HLA I). Dominant peptides exhibit high HLA I affinity and immunogenicity but most vaccines targeting dominant peptides gave relatively disappointing results in clinical studies due to the presence of tolerance. One simple way to break tolerance to tumor antigens is to use cryptic peptides. Indeed, we and others have shown that the T-cell repertoire specific for cryptic peptides partially or completely escapes tolerance mechanisms, suggesting that cryptic peptides would be good tumor vaccines provided they are rendered immunogenic. Cryptic peptides, which have low HLA class I affinity and therefore are not immunogenic, have to be “optimized” by modifying their amino acid sequence to increase their HLA class I affinity thereby transforming them into high-affinity peptides capable of stimulating a specific T-cell immunity but not autoimmunity in HLA-A*0201 transgenic mice.

In vitro, TERT572Y stimulated antitumor CTLs from both healthy donors and prostate cancer patients; CTLs killed TERT-expressing tumor cells but not TERT-expressing normal cells. Vx-001 has recently been tested in a phase I clinical study in 19 patients with advanced cancer. Vx-001 was safe (only grade I/II toxicity was observed) and immunogenic. TERT572 specific immune response was detected in 13 out of 14 evaluable patients. As part of an expanded phase I clinical study, 16 patients with advanced cancer. Vx-001 was safe (only grade I toxicity was observed) and immunogenic. TERT572 specific immune response was detected in 13 out of 14 evaluable patients. As part of an expanded phase I clinical trial, 16 patients with advanced NSCLC were vaccinated with Vx-001 and their clinical outcome was compared with that of 15 case-matched historical control patients with similar disease and treatment characteristics. Here we report that in vaccinated patients, the vaccine was safe and immunogenic, generating functional CTLs which recognize the native TERT572 peptide. More importantly, patients with early developed immunological response had a significantly better overall survival than those without an immunological response.

Vaccination protocol

Objectives:
- Primary: Safety and immunogenicity of (Vx001) vaccine
- Secondary: Time to progression (TTP), overall survival and survival

Patients: HLA-A*0201 expressing NSCLC

Protocol:
- TERT572Y
- TERT572

Safety in vaccinated patients

Clinical response of vaccinated patients

Correlation Between TTP and Early Immune Response

Survival of Vaccinated Patients and Matched Controls

Conclusions

- Vx-001 was safe and immunogenic in almost all vaccinated patients.
- Patients who developed early immune response had a significantly better clinical outcome. TTP and survival than patients who did not. This difference was observed between early immune responders and non-responders, despite similar stable disease patient ratio at inclusion.
- Based on these encouraging results, we are planning a controlled multicentric study to evaluate the clinical benefit of Vx-001 vaccination in NSCLC patients.