Original Study

Feasibility Study of Personalized Peptide Vaccination for Advanced Small Cell Lung Cancer

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Abstract

We conducted a phase II study of personalized peptide vaccination (PPV) for 46 patients with advanced small cell lung cancer (SCLC). We observed immune boosting and possible prolongation of overall survival after PPV without severe adverse events. These results suggest that PPV has potential as a new treatment modality for SCLC.

Introduction: The prognosis of patients with small cell lung cancer (SCLC) remains very poor. Therefore, the development of new therapeutic approaches, including immunotherapies, is desirable. **Patients and Methods:** We conducted a phase II study of personalized peptide vaccination (PPV), in which a maximum of 4 human leukocyte antigen-matched peptides were selected from 31 pooled peptides according to the pre-existing peptide-specific IgG responses before vaccination. The PPV was subcutaneously administered. **Results:** Forty-six patients were enrolled (median age, 63 years; 40 patients were men). Grade 1 (n = 13), 2 (n = 10), or 3 (n = 1) skin reactions at the injection sites were observed; however, no other severe adverse events related to the PPV were observed. The median survival time was 466, 397, 401, and 107 days in the subgroups with 0 (n = 5), 1 (n = 15), 2 (n = 12), and ≥ 3 (n = 14) previous chemotherapy regimens, respectively. Peptide-specific IgG responses to the vaccinated peptides were augmented in 70% and 95% of patients after 1 and 2 vaccination cycles, respectively. The overall survival (OS) of patients with augmented IgG responses to a greater number of nonvaccinated peptides after the second cycle of vaccination was significantly longer (median survival time, 1237 days vs. 382 days; $P = .010$). In addition, augmentation of IgG responses specific to 6 peptides, including Lck-derived peptides, was significantly related to better OS ($P < .05$, in each peptide). **Conclusion:** These results suggest the feasibility of PPV for SCLC patients from the viewpoints of safety, immune boosting, and possible prolongation of OS. Therefore, further evaluation of PPV for advanced SCLC in prospective randomized trials is warranted.

Clinical Lung Cancer, Vol. ■, No. ■, ■-■

Keywords: Epitope spreading, IgG, Lck, PPV, SCLC

Introduction

Lung cancer is the leading cause of cancer-related deaths globally, and small cell lung cancer (SCLC) accounts for approximately 13% of all lung cancer cases.[1] SCLC is an aggressive neuroendocrine malignancy and has features of a short doubling time, high growth fraction, and early development of widespread metastases.[2] Therefore, patients with SCLC have a very poor prognosis. Moreover, although many clinical trials of targeted therapies and newer

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Submitted: Jan 11, 2017; Revised: Mar 15, 2017; Accepted: Mar 15, 2017

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http://dx.doi.org/10.1016/j.cllc.2017.03.011

chemotherapeutic agents have been conducted, no effects were obtained compared with standard therapy.[2] Thus, a need exists for newer therapeutic approaches. One such approach might be blockade of the T-cell inhibition mediated by the checkpoint molecules, such as programmed death 1 and programmed death ligand 1, in SCLC patients, because the expression of programmed death ligands 1 and 2 has been observed in the tumor microenvironment of SCLC.[3] Another new approach might be personalized therapeutic agents. Along this line, we developed a novel regimen of personalized peptide vaccination (PPV), in which peptides are selected and administered according to the pre-existing host immunity before vaccination. In the present study, we investigated the feasibility of PPV for SCLC patients.

Patients and Methods

Patients

Patients with a diagnosis of advanced SCLC were eligible for the present study. All patients were required to have a diagnosis of limited-stage SCLC, extensive-stage SCLC, or recurrent-at-diagnosis disease. In addition, the patients were required to have positive IgG responses to $\geq$ 2 of the 31 different vaccine candidate peptides, as reported previously.[4-6] The other inclusion criteria were Eastern Cooperative Oncology Group performance status of 0 or 1 at the first visit, positive status for human leukocyte antigen (HLA)-A2, -A24, -A3 supertype (A3, A11, A31, or A33), or -A26 types, life expectancy of $\geq$ 12 weeks, and adequate hematologic, hepatic, and renal function. The exclusion criteria were pulmonary, cardiac, or other systemic diseases; acute infection; a history of severe allergic reactions; pregnancy or nursing; and other inappropriate conditions for enrollment as judged by the clinicians. The Kurume University and Sendai Kousei Hospital ethical committees approved the protocol, which was registered in the University Hospital Medical Information Network (UMIN) Center Clinical Trials Registry (UMIN nos. 1482, 1839, 2984, 6927, 10068, and 11230). All patients were given a full explanation of the protocol and provided their informed consent before enrollment.

Clinical Protocol

We performed a phase II study to evaluate the safety, immunologic responses, and clinical benefits with the endpoint of overall survival (OS) in advanced SCLC patients receiving PPVs. We used 31 peptides for vaccination (12 peptides for HLA-A2, 16 peptides for HLA-A24, 9 peptides for HLA-A3 supertypes [HLA-A3, -A11, -A31, and -A33], and 4 peptides for HLA-A26), as previously reported (Supplemental Table 1; online version).[4-6] These peptides were prepared in accordance with the conditions of Good Manufacturing Practice by PolyPeptide Laboratories (San Diego, CA) and American Peptide Company (Vista, CA). The peptides for vaccination of individual patients were selected by considering the pre-existing host immunity before vaccination, as assessed by the titers of IgG specific to each of the 31 different vaccine candidates.[7-11] A maximum of 4 peptides (3 mg/each peptide), which were selected according to the results of HLA typing and peptide-specific IgG titers, were subcutaneously administered with incomplete Freund's adjuvant (Montanide ISA51; Seppic, Paris, France).

Figure 1 Flow Chart of Different Personalized Peptide Vaccination (PPV) Regimens Regarding Numbers and Intervals of Peptide Administration