Personalized peptide vaccination for advanced colorectal cancer

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Keywords: biomarker, colorectal cancer, IL-6, peptide vaccine, personalized vaccine

Abbreviations: aCRC, advanced colorectal cancer; CTL, cytotoxic T lymphocyte; HR, hazard ratio; OS, overall survival; PPV, personalized peptide vaccination.

Introduction

Recent advances in chemotherapy and/or targeted therapy have improved clinical outcomes in patients with advanced colorectal cancer (aCRC); however, the prognosis remains poor. The development of new therapeutic approaches, including immunotherapy, is thus urgently needed. However, limited numbers of clinical trials of immunotherapies have been reported for patients with aCRC. We have developed a novel approach in cancer immunotherapy, the personalized peptide vaccination (PPV), in which human leukocyte antigen (HLA)-matched peptides are selected on the basis of preexisting host immunity before vaccination. Recently, we demonstrated the feasibility of PPV in previously treated patients with advanced colorectal cancer, thus warranting further clinical development of this approach.

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The median overall survival (OS) time from the first vaccination was 498 d (95% CI, 233–654 days) from the first vaccination, suggesting a potential survival benefit of PPV in previously treated patients with aCRC, even in the refractory stage. Boosting of CTL responses specific to the administered peptides was observed in 63% of patients who completed the first cycle of 6 vaccinations. Importantly, increased peptide-specific CTL responses after vaccination were significantly predictive of favorable OS independently of other factors, suggesting a causal relationship between the biological and clinical efficacies of PPV.

Several post-vaccination biomarkers, such as immune (CTL and/or immunoglobulin G [IgG]) responses to the vaccine antigens, delayed-type hypersensitivity, and autoimmunity, have been reported to be associated with clinical responses in cancer immunotherapies;¹² however, there are currently no validated pre-vaccination predictive biomarkers in widespread use. Not all patients showed clinical benefits from PPV; therefore, we tried to identify prognostic or predictive biomarkers in patients with aCRC who...
were treated with PPV. By the Cox proportional hazards model, higher interleukin (IL)-6 and interferon gamma-inducible protein-10 (IP-10) and lower B-cell activating factor (BAFF) levels in pre-vaccination plasma were significantly associated with unfavorable OS (hazard ratio [HR] = 1.508, \( P = 0.043 \); HR = 1.579, \( P = 0.024 \); HR = 0.509, \( P = 0.002 \); respectively), although these factors might be not necessarily be predictive and unique to PPV. Notably, however, the pre-vaccination IP-10 level was predictive of the increase in CTL responses (odds ratio, 0.427; \( P = 0.039 \)), which was associated with improved OS after vaccination, suggesting that IP-10 might potentially be useful for selecting patients with aCRC who would benefit from PPV. To more clearly assess the causal relation of IP-10, CTL responses, and OS as well as to elucidate prognostic versus the predictive relevance of such biomarkers, future randomized, controlled clinical trials with or without PPV would be required.

We have demonstrated that IL-6 might be useful for predicting OS in PPV-treated patients with various types of cancers including aCRC. As IL-6 has recently been reported to induce suppressive immune cell subsets, such as myeloid-derived suppressor cells and Th17, high levels of IL-6 may inhibit immune responses to cancer vaccines by inducing these suppressive cells. Based on these findings, an early-phase clinical trial is underway to examine whether inhibition of IL-6-mediated inflammatory signaling with a humanized anti–IL-6 receptor monoclonal antibody, tocilizumab, would be beneficial for enhancing the immune and/or clinical responses after PPV in patients with aCRC who show higher plasma IL-6 levels. Interestingly, we demonstrated that the IL-6R 48892A>C polymorphism might have a significant effect on OS in patients with aCRC after PPV: the patients bearing the IL-6R 48892C/C or 48892A/C genotypes tended to have a better prognosis than those carrying the IL-6R 48892A/A genotype. As the IL-6R 48892A>C polymorphism has been reported to show no effects on prognosis in patients with some cancers, such as esophageal squamous cell carcinoma and neuroblastoma, without cancer vaccines, the prognostic significance of this polymorphism might be unique to vaccinated patients.

In summary, our recently conducted phase 2 trial demonstrated that PPV induced substantial immune responses to vaccine antigens without severe adverse events and showed a potential clinical benefit in previously treated patients with aCRC even in the refractory stage. Nevertheless, because it was a small study with a limited number of patients, some of whom received combined chemotherapies and/or targeted therapies during the vaccination period, the clinical efficacy of PPV, as well as the clinical utility of the identified biomarkers, in patients with aCRC remain to be confirmed in future, larger scale, randomized trials of PPV without combined chemotherapies or targeted therapies.

Disclosure of Potential Conflicts of Interest

Kyogo Itoh owns stock in the Green Peptide Co., Ltd., and has received research funding from Taiho Pharmaceutical Co., Ltd. No potential conflicts of interests were declared by the other authors.

Funding

This study was supported by funding to a research program of the Project for Development of Innovative Research on Cancer Therapeutics (P-Direct) of the Ministry of Education, Culture, Sports, Science and Technology of Japan.
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