ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Potential Anticancer Benefits of Peptide Vaccines

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H&O Can you briefly review peptide vaccines in cancer?

YN Peptide vaccines fall broadly into the category of defined-antigen vaccines, along with vaccines using protein, protein subunits, DNA, or RNA. They incorporate 1 or more short or long amino acid sequences as tumor antigens, combined with a vaccine adjuvant. Peptide vaccines rely on the immunogenic properties of certain cancer-associated peptides to begin a cascade of destructive events against a tumor. This type of treatment offers the promise of inducing T cells reactive to well-characterized tumor antigens, as well as enabling the assessment of vaccination effect by monitoring antigen-specific T-cell responses. Cancer cells express peptide antigens recognized by CD8+ cytotoxic T lymphocytes (CTL), which are typically 9–10 amino acids long and are presented in association with class I major histocompatibility complex (MHC) molecules. The peptides recognized by helper (CD4+) T cells are presented in association with class II MHC molecules and are usually longer (13–18 amino acids in length), although peptide elution studies have indicated no apparent restriction on peptide length.

H&O Compared to other therapeutic strategies, why are peptide vaccines an attractive treatment option?

YN Peptide vaccine treatment is quite different from conventional chemotherapy. Peptide vaccines offer a potential anticancer benefit with very little risk of toxicity. Most patients have a grade 1 or 2 local toxic response, which typically includes redness at the injection site. Some patients experience grade 1 or 2 systemic symptoms, mostly in the form of minor flu-like symptoms for 4–6 hours after receiving the vaccine. However, systemic reactions are rarely seen with the use of peptide vaccines. The mode of function is quite different from chemotherapy because the vaccine can increase the number of T cells that can kill cancer cells, but 1 stimulation or 1 injection can very moderately increase the number of killer T cells, so we have to administer injections repeatedly. At present, there are more than 50 cancer vaccine treatments being investigated in phase I, II, and III clinical trials. Results of some trials are anticipated within the next 2–3 years.

H&O What is known about the use of multiple peptides as a therapeutic strategy?

YN We started translational research approaches with a single peptide, and now we are using a cocktail of up to 7 peptides. In colon cancer, 2 peptides were originally used, but this rarely resulted in tumor shrinkage. Now, we are testing a mixture of 7 peptides, which has led to an average of 1 in 10 patients achieving tumor shrinkage. It is generally believed that treatment efficacy will be enhanced when original molecules of vaccines function as essential molecules for cancer cell survival, proliferation, and/or motility. Some success has already been demonstrated with the use of multipeptide vaccines in areas like esopha-

geal and colorectal cancer. Identifying CTL-inducible epitope peptides derived from several molecules that play critical roles in various types of cancer will be important for the development of future multipeptide cocktails.

H&O What are some of the biggest obstacles in peptide vaccine development?

YN A major challenge is how the effects of vaccines are evaluated by oncologists, as it is different from methods used to evaluate other anticancer therapies. Even if no tumor shrinkage is observed during a clinical trial of immunotherapy, this does not mean that the particular immunotherapy is ineffective. Hence, a longer observation period is needed to examine the clinical effects of vaccines, especially for patients with larger-sized tumors. Considering the kinetics of the activated T cells by vaccine, several months may be required before there is any antitumor effect. In general, early-stage trials involving vaccine treatments enroll patients with advanced-stage disease who have failed previous chemotherapy. Their survival is not usually long enough for us to observe clinical benefit from vaccination. Thus far, peptide vaccines have not shown a tremendous effect on progression-free survival, and we have to monitor patients for many years before we can see differences in overall survival.

H&O What are some promising areas of research that you are involved with?

YN We are developing a small molecular compound and we are also testing an antibody drug. For this antibody drug aimed at treating synovial sarcoma, we had a very difficult time obtaining funding for a clinical trial in Japan. However, Dr. Jean-Yves Blay, the current president of the European Organisation for the Research and Treatment of Cancer (EORTC), went to great lengths to support the clinical trial, which began in January 2012. We expect to finish the phase I portion within a year. We are also working on a small molecular compound that is aimed at targeting cancer stem cells, mainly breast cancer stem cells. We hope to begin a clinical trial for this compound within a few months at the University of Chicago.

H&O What are the biggest remaining challenges?

YN Typically, we provide vaccination to patients who are in very advanced stages of disease and who have already received at least 1 regimen of chemotherapy. However, it would be more ideal to provide a cancer peptide vaccine to patients at an earlier stage, including those with minimum metastatic disease, or to prevent recurrence in patients who show no signs of metastasis following a surgical procedure. Patients with smaller tumors are expected to have a greater benefit from vaccine treatment because we do not need to increase the large number of T cells as much as we would need to for patients with larger tumors.

H&O What do you think the future holds?

YN Several new developments offer promise for improving peptide vaccines, including the use of long peptides, optimization of adjuvants (including toll-like receptor agonists), and combination approaches with systemic therapies that may reduce tumor-associated immune dysfunction, such as the blockade of PD-1/PD-L1 interactions. To apply these new approaches most effectively, it will be critical to study their effects in the context of defined antigens, for which peptide vaccines appear to be optimal. I am quite confident that cancer peptide vaccines will become one of the major treatment options in the near future.

Suggested Readings

Kono K, Iinuma H, Akutsu Y, et al. Multicenter, phase II clinical trial of cancer vaccination for advanced esophageal cancer with three peptides derived from novel cancer-testis antigens. *J Transl Med*. 2012;10:141.

Sawada Y, Yoshikawa T, Nobuoka D, et al. Phase I trial of a glypican-3–derived peptide vaccine for advanced hepatocellular carcinoma: immunologic evidence and potential for improving overall survival. *Clin Cancer Res*. 2012;18:3686-3696.

Okuno K, Sugiura F, Hida J, et al. Phase I clinical trial of a novel peptide vaccine in combination with UFT/LV for metastatic colorectal cancer. *Exp Therapeutic Med*. 2011;2:73-79.