ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Cancer Vaccines

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H&O What are some recent developments in tumor vaccines?

YN The goal of tumor vaccines, a type of immunotherapy, is to stimulate the immune system in order to recognize and eliminate cancer cells. There are various strategies in immunotherapy; some use cancer cells from the patient, some use cancer cell lines, and others use proteins and peptides. Immunotherapy has been viewed as an experimental therapy until very recently. In April 2010, sipuleucel-T (Provenge, Dendreon) was approved for men with advanced prostate cancer. This regulatory approval provided some proof that immunotherapy could be used for treatment of cancer, and in the next 5–10 years, we expect many therapeutic cancer vaccines to be approved. At present, there are approximately 20 multiple type vaccines (ie, cancer cell-, protein-, and peptide-based vaccines) being investigated in phase III trials. This discussion will focus on peptide-based vaccines.

H&O Why are vaccines an attractive option for cancer treatment?

YN I think there is interest in cancer vaccines as anticancer therapeutics because they have very limited side effects. Although many patients may develop local reactions at the injection site when vaccines are administered subcutaneously or intradermally, systemic reactions are rarely seen. Further, I believe that cancer vaccines will improve quality of life compared to most of the anticancer therapies.

At present, an important consideration in cancer treatment is quality-adjusted life years. Generally, oncologists are concerned with overall survival or tumor shrinkage when evaluating drug efficacy; however, it is also important to consider the quality of life of the patient, which may be better with immunotherapy. This is something to keep in mind when developing next generation anti-cancer therapies.

H&O What are the challenges seen in cancer vaccine development?

YN One of the challenges is convincing oncologists of the way to evaluate the effect of cancer vaccines, as it is different from that used to evaluate anti-cancer therapies. During a clinical trial of immunotherapy, even if no tumor shrinkage is observed, this does not mean that the therapy is not effective. It is particularly difficult to convince oncologists of this idea in Japan. Another limitation that is encountered is the need for a longer period of time to see effects of immunotherapy. Because of the time it takes to increase the number of cytotoxic T cells, especially for patients with larger tumors, more time is needed to observe benefit. Considering the kinetics of the activated T cells by vaccine, antitumor effect may take up to several months. In general, early-stage clinical trials for cancer therapies that include vaccine treatment can only enroll patients who have failed previous chemotherapy and who have advanced-stage disease. Because these patients are in advanced disease, their survival is usually not long enough for us to be able to see the effects from vaccination, especially if longer follow-up is necessary.

H&O Is there evidence of synergy between vaccines and chemotherapy?

YN Vaccines and chemotherapy have been administered concurrently to treat cancer, and such combinations are actively being investigated. However, there are some concerns because cytotoxic anticancer drugs naturally cause immunosuppression while the tumor vaccine enhances the immune response. However, many doctors feel that there is some synergistic effect between chemotherapy and cancer vaccine treatment given to patients with good performance status.

Our laboratory is involved in translational research evaluating cancer vaccines in various tumors. In the last 5 years, we have enrolled 1,600 patients; in our analysis of these patients we have seen evidence of synergy between chemotherapy and immunotherapy. Some examples of vaccine and chemotherapy combinations include gemcitabine and vaccination for pancreatic cancer and tegafur-uracil plus vaccination for colon cancer.

H&O At what point should a vaccine be administered?

YN Ideally, we would provide cancer vaccines in the adjuvant setting or even in patients with minimum metastatic disease because the number of the cancer cells is small enough. The number of cancer cells of a 10-cm tumor is estimated to be approximately 10^{11}. It is very difficult to increase the number of vaccine-specific cytotoxic T cells to this level. We should be providing chemotherapy and immunotherapy concurrently in the early stages of disease. If we are to expect a clinical effect of a vaccine as a single therapy, we should try to select a patient population with minimal tumor burden and use overall survival as the endpoint.

H&O What kind of patient population is ideal for vaccines?

YN We have been providing vaccination to patients with very advanced disease after at least 1 regimen of chemotherapy. However, vaccine therapy should ideally be given to patients with minimum metastatic disease or to prevent recurrence in patients who, after a surgical procedure, have no signs of metastasis. Patients with smaller tumors (eg, 1 cm) are expected to have benefit from cancer vaccines because we do not need to increase the large number of T cells as much as we would need to for someone with a tumor that was 10 cm.

H&O What kind of research are you involved with?

YN Recently, we had a meeting of the Cancer Peptide Vaccine Translational Research Network, which is made up of members from approximately 60 hospitals in Japan. Five years ago, our members accepted the idea that cancer vaccines could be a viable treatment approach, and our study results from 2 years ago further solidified this possibility. At this year's meeting, we have presented additional evidence that cancer vaccines will be established as a cancer treatment in the near future. In addition to the research being done by our group, various Japanese companies are running clinical trials of cancer vaccines for pancreatic, bile duct, esophageal, and bladder cancers.

Suggested Readings

Lesterhuis WJ, Haanen JBAG, Punt CJA. Cancer immunotherapy-revisited. *Nat Rev Drug Discov.* 2011;10:591-600.

Schwartzentruber DJ, Lawson DH, Richards JM, et al. Mgp100 peptide vaccine and interleukin-2 in patients with advanced melanoma. *N Engl J Med.* 2011;364: 2119-2127.

Miyazawa M, Ohsawa R, Tsunoda T, et al. Phase I clinical trial using peptide vaccine for human vascular endothelial growth factor receptor 2 in combination with gemcitabine for patients with advanced pancreatic cancer. *Cancer Sci.* 2010:101:433-439.