

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Breast Cancer In Focus

HER2 Vaccination in High-risk Breast Cancer

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H&O What is E75 and how does it work?

GP Our group has been investigating vaccines that target HER2/neu for approximately 15 years. E75 is a 9 amino acid peptide from HER2/neu and is the peptide most recognized by the immune system from this protein. The vaccine is meant to stimulate CD8 positive cytotoxic lymphocytes to recognize and kill anything that expresses the peptide, which is usually found in very high concentrations on cancer cells that express the HER2/neu protein. The vaccine is composed of the peptide in combination with an immune system stimulant, granulocyte macrophage-colony stimulating factor (GM-CSF), given as an intradermal injection once a month for 6 months. The vaccine generates immunity against HER2/neu, and by raising this immunity in the adjuvant setting, we can determine whether or not the vaccine will prevent recurrence.

The majority of clinical trials with cancer vaccines have been done in the same manner as that in which cytotoxic agents have been tested, where late stage metastatic patients are tested in a dose-escalating type strategy for safety endpoints. The problem with choosing this strategy for vaccine trials is that these trials employ some form of immunotherapy, in this case an active specific immunotherapy—vaccination—to try to stimulate the immune system to react against cancer in the presence of a large burden of cancer. In contrast, our group has tested vaccines in the adjuvant setting as a preventative measure. Because of the difficulty of running a true pre-

vention trial in cancer naive patients, we work primarily in the adjuvant setting. In our studies, we enroll patients that are disease-free and have an intact immune system. These patients can be vaccinated during their disease-free interval, and this gives us a defined period of time in which to determine whether there is any benefit to the patient, because we know the recurrence rates over a specific time frame. Although this approach is secondary prevention, it is still a way of utilizing the vaccine as prevention as opposed to as therapy for a metastatic patient.

H&O What do we know of the benefits and challenges of the vaccine?

GP There are distinct advantages of active specific immunotherapy over passive immunity like a monoclonal antibody that interferes with HER2/neu (ie, trastuzumab). For example, when trastuzumab (Herceptin, Genentech) is terminated it has no residual effect, whereas the vaccine is meant to engage the endogenous immune system—it helps produce long term and protective immunity. What is also beneficial about the vaccine is that it has a different mechanism of action from trastuzumab, and thus requires less HER2 expression. Seventy-five percent of breast cancers express some level of HER2 expression, whether it is low, intermediate, or high, and the vaccine is effective in all of these levels. E75 is therefore applicable to a much larger group of women than trastuzumab, which requires women to have the highest level of HER2 expression.

Part of the challenge we now face is the divide between therapeutic and preventative vaccines. As previously mentioned, the majority of research has gone into the therapeutic area, and because there have been some notable failures in phase III clinical trials in this arena,

there now exists some bias against cancer vaccines in general. Thus, our challenge has been in re-educating people about the adjuvant vaccination strategy and why it differs from the failures that have occurred in the past. I believe that the adjuvant setting is going to be the area where vaccines get the most traction. However, what is happening right now in the metastatic and therapeutic trials is that although the immune system may not have a direct impact on the size of the tumor or the burden of disease, it is affecting longevity (ie, Provenge trial).

H&O Are there any long-term data with E75?

GP The adjuvant trials that we have run with the E75 peptide have produced some interesting long-term results. The median follow-up of the trials are now more than 4 years; we are closing in on the conclusion of these trials, which have a 5-year follow-up endpoint. The trials enrolled approximately 200 patients, half of whom were vaccinated and half who were followed prospectively as controls to determine whether or not there was a clinical benefit to E75 plus GM-CSF vaccination. The study was not randomized; selection between who was to be vaccinated and who was to be control was based on human leukocyte antigen (HLA) type. Specific HLA type is required because of the peptide-based vaccine, which is a limitation of this strategy; however, peptide vaccines are potent, inexpensive, easily disseminated, and easily manufactured. Fortunately, HLA-A2 is the most common HLA type in the United States; approximately half of the population carries that allele. Thus, E75 was administered to patients who were HLA-A2 positive; HLA-A2 negative patients were followed as controls.

The study was initiated in 2001 and half of all patients have completed 4-year follow up. The study findings show that in the vaccinated population, there has been an approximate 40% reduction in recurrence. What we have learned from this trial and incorporated into our ongoing trials is the requirement to boost the vaccine. Similar to the booster inoculation administered for hepatitis vaccines, the cancer vaccines require boosting as well. Earlier in the trial, we did not include booster inoculations, and as the immunity to HER2/neu waned, we began to see more recurrences in the vaccine arm. We initiated the booster program approximately 3 years ago, and anyone who enrolled after that period of time was given boosters every 6 months as part of their vaccination series. Thus, half of the vaccinated patients received boosters and half did not. Among the patients that received the boosters, there has only been 1 recurrence. The numbers are small, and therefore it is hard to make a strong statement, as there is no statistical significance; however, the trend is showing a substantial reduction in recurrences with vaccination and booster inoculations.

H&O Are there any side effects to this vaccine?

GP Vaccines are inherently safe. In all of our trials, we have never had more than 20% grade 2 type reactions. The vaccination is similar to getting a flu shot. For the most part, there is no systemic toxicity, and the safety has never really been an issue.

H&O What do we know about combinations of anti-HER2 agents and vaccines?

GP Preclinical data published by my colleagues and I have shown that there is a synergistic effect between the vaccine and trastuzumab. We currently have an ongoing phase I trial investigating such a combination. The study is enrolling patients who are receiving trastuzumab therapy, and adding vaccinations to their regimen to determine whether a clinical benefit can be seen. Another group that studies similar vaccines is from the University of Washington, led by Mary Disis. Her group also works with HER2/neu, but instead of solely targeting CD8, their vaccines target CD4 as well. Dr. Disis and colleagues recently published a paper in the *Journal of Clinical Oncology* that has shown the safety of using the HER2 vaccine in combination with trastuzumab. They found that the combination is safe with no increase in cardiotoxicity, and that it improves long-term immunity. If this long-term immunity translates into long-term clinical benefit, this will be very exciting news, but this we do not know yet.

H&O How far are we from being able to administer the vaccine outside of clinical trials, and what do we hope to achieve with its approval?

GP The E75 vaccine (now called NeuVax) is licensed to a biotechnology company (Apthera, Scottsdale, AZ) that is orchestrating the activities around the phase III trial that will be conducted for product approval from the Food and Drug Administration (FDA). This process is initiated through a special protocol assessment, where the FDA will have input into the product and trial design. In essence, they assist in designing a trial that will result in an approvable product, which is not approved until the FDA sees the data. In the case of E75, this process has been completed, and the trial design has been approved. The study will target very high-risk breast cancer patients (ie, node-positive patients). Instead of separating HLA-A2 positive versus negative patients, the study will only include HLA positive patients. Patients will be randomized to receive either the vaccine (E75 with GM-CSF) or the immunoadjuvant alone (placebo). The study will be double-blinded and prospective. It

will enroll 700–900 patients and will be performed in multiple institutions, with the possibility of a cooperative group taking the lead on the trial. The primary endpoint will be recurrence rate or disease-free survival at 3 years. The trial will target women with low and intermediate expression, with the idea that in the adjuvant setting, women who have an overexpression of HER2/neu already have a therapeutic option (trastuzumab), whereas the low/intermediate expression groups do not. We anticipate that the trial will commence next year and will take approximately 2 years to enroll patients, with a median of 3-year endpoints. We expect to complete the study by 2015.

If the vaccine gets FDA approval, the hope is that it will be approved as an adjuvant agent in high-risk breast

cancer, providing women with low and intermediate HER2 expression a treatment option they previously did not have.

Suggested Readings

Peoples GE, Holmes JP, Hueman MT, et al. Combined Clinical Trial Results of a HER2/neu (E75) Vaccine for the Prevention of Recurrence in High-Risk Breast Cancer Patients: U.S. Military Cancer Institute Clinical Trials Group Study I-01 and I-02. *Clin Cancer Res.* 2008;14:797-803.

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