

Cancer Vaccines: The Role of Tumor Burden in Tipping the Scale Toward Vaccine Efficacy

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Cancer vaccines have significant theoretical therapeutic advantages over more standard methods of cancer treatment. If a robust cellular immune response could be elicited, then immunologic memory could be long lasting, eradicating cancer at times quite distant from initial therapy. T cells potentially can migrate to tumor sites, leave the vasculature, and invade tissues eradicating deep-seated disease at any metastatic site. Furthermore, T cells are extremely specific in their attack, as opposed to the generalized toxicities seen with some chemotherapies. Finally, as long as there is antigen available for T-cell recognition, T cells have the potential to continue to respond until disease is eradicated. In this issue of the *Journal of Clinical Oncology*, investigators from Walter Reed Army Medical Center (Washington, DC) and the M.D. Anderson Cancer Center (Houston, TX) present data from a trial in which breast cancer patients were immunized with a vaccine targeting the HER-2/*neu* oncogenic protein to prevent disease relapse.¹

Many recent clinical trials of cancer vaccines, such as the one reported in this issue by Peoples et al,¹ demonstrate that a majority of cancer patients can develop measurable immune responses directed against specific tumor antigens after active immunization. Although the ability to detect tumor antigen-specific immunity seems like a small first step in the clinical application of cancer vaccines, it is a significant one because most tumor antigens are self, and tolerance to self should limit such immunity. A decade ago it was commonly assumed that immunogenic proteins expressed by tumors would be mutated in some way. Therefore, widely studied candidate antigens included molecules such as mutated ras or p53.

We now know that many nonmutated cancer-related proteins, such as HER-2/*neu*, are immunogenic in cancer patients. What makes HER-2/*neu* immunogenic? A probable explanation may be found in the overexpression of the protein in tumor cells, compared with noncancerous cells,

which express basal levels of HER-2/*neu*. Increasing the level of an antigen in a tumor cell above what is present in nonaffected cells may allow more efficient processing of that protein by antigen-presenting cells, resulting in the development of an immune response.² Although endogenous immunity can be elicited in cancer patients by virtue of their tumors overexpressing a protein, the generated immune response obviously is not capable of preventing tumor growth. Several factors may play a role in inhibiting the antitumor efficacy of endogenous immunity, including the immunosuppressive environment of the tumor,³ the low avidity of the T cells for the antigen expressed on the tumor, and the low magnitude of the endogenous immune response.⁴ Theoretically, cancer vaccines designed to augment tumor-specific cellular immunity could at least partially overcome these defects by both boosting low-level immunity and stimulating the proliferation of higher avidity T cells capable of homing to a tumor.⁴

Modern methods of detecting antigen-specific T-cell responses have allowed a more complete analysis of the potency of cancer vaccines. Peoples et al¹ used a highly quantitative assay, HLA-A2/immunoglobulin dimer, which allowed them to specifically evaluate the *in vivo* expansion of CD8⁺ T cells directed against a particular HER-2/*neu* peptide used for vaccination. Such an assay simulates the peptide-major histocompatibility complex so that only T cells with the prescribed specificity can be measured. Given that the vaccine described here was specific for an HLA-A2 peptide derived from HER-2/*neu*, the quantitative method was ideal for measuring the type of immunity elicited with that particular vaccine. During the last few years, a variety of highly quantitative, reproducible immune assays have been developed that allow rigorous assessment of the immunologic effect of cancer vaccination.⁵ Methods such as the dimer and tetramer assays entail exquisite enumeration of antigen-specific T cells without regard to their functional

status. Other means of analysis such as enzyme-linked immunospot assay and intracellular cytokine staining will specifically quantitate functional T cells responding to antigen. These assays have greatly facilitated vaccine development and optimization, yet measuring the effects of vaccination on the immune system cannot be considered a surrogate for a clinical response.

A recent review evaluated the clinical outcomes of cancer vaccines and cited therapeutic response rates associated with vaccination ranging from 1.9% to 9.5%, depending on the construction of the vaccine.⁶ When one considers the incredible hurdles that must be overcome to elicit therapeutic antitumor immunity, it is a wonder any clinical activity could be detected in these tumor-bearing patients.⁷ Clearly, therapeutic cancer vaccines have limited potential as single agents in advanced-stage disease. Peoples et al¹ explore the possibility of therapeutic vaccines preventing cancer relapse in the adjuvant setting with presumed minimal residual disease. Vaccines against infectious agents have had enormous impact on human health in disease prevention. An open question is whether cancer vaccines will have a role in prevention of relapse in minimal residual disease or should only be evaluated as chemoprevention agents in high-risk patients who have never developed malignancy.⁷ Is there a critical mass of tumor cells beyond which vaccination is futile? The provocative data presented by Peoples et al would suggest that the therapeutic success of cancer vaccines might lay in the choice of patients, such as those with minimal rather than bulky disease. Determining whether therapeutic cancer vaccines have any role in cancer treatment will be accomplished only by well-designed and controlled clinical trials with uniform types of patients, robust patient numbers, and an adequate length of follow-up. Such trials take a commitment of both resources and time. Early-

stage studies designed to provide both preliminary immunologic and clinical data can make the decision to invest those resources much easier.

Cancer is immunogenic, the defects limiting the endogenous tumor-specific immune response are being defined in increased detail, and patients can be immunized against their tumors. The last several years have yielded incredible insight into the interaction of the immune system with human malignancy. The question before us now is whether cancer vaccines can become part of our therapeutic armamentarium, and if so, for what stage of disease?

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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