Immunizing against breast cancer: A new swing for an old sword

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Cancer vaccines based immunotherapy should potentiate immunosurveillance function preventing and protecting against growing tumors. Tumor cells usually activate immune system, including T lymphocytes and Natural Killer (NK) cells, which are able to eliminate the transformed cells. Immunosubversion mechanisms related to tumor cells antigenic immunoediting induces mechanisms of tolerance and immunosuppression. This condition impairs not only host-generated immunosurveillance, but also attempts to harness the immune response for therapeutic purposes. Most trials evaluating breast cancer vaccines have been carried out in patients in the metastatic and adjuvant setting. It is difficult to demonstrate vaccine activity because traditional end points of cancer therapy (e.g., response, tumor regression) cannot be applied to vaccine therapy. Using conventional criteria for clinical tumor response, objective response rate in cancer vaccines trials was only 2.6%, which is similar to the overall response rate we determined in a detailed analysis of cancer vaccine trials performed by others. This low clinical effectiveness raises important questions about the appropriate directions for future clinical immunotherapy efforts, especially at a time when alternative approaches such as cell transfer studies confirm the powerful potential of immunotherapy to mediate the regression of large volumes of metastatic disease in experimental models and in humans. The lessons we have learned from the first studies is that the vaccine could achieve the better results in patients with minimal disease or in the adjuvant setting. The use of cancer vaccines is particularly promising in early-stage because in this group of patients the immunosuppressive effect of bulky disease does not overpower the immune system and the effector–target ratio is then favorable.

We need to better select the patient population and to introduce a standard of regulatory guidelines to reach immune responses. Optimal combination vaccination therapy with a variety of novel approaches (e.g., monoclonal antibody or tyrosine kinase inhibitors) is a great promise but it also requires evaluation in clinical trials to assess its benefit. Therapeutic cancer vaccines should be investigated in 2 general types of clinical studies: proof-of-principle trials and efficacy trials. Proof-of-principle trials, which introduce a novel cancer vaccine into humans, should include a minimum number of patients in a homogenous, well-defined population in an adjuvant setting or in patients without rapidly progressive disease in a metastatic setting to allow vaccines adequate time to induce biologic activity and should incorporate immune and molecular surrogate markers. Aims of these studies should include safety and feasibility in order to provide determination of dose and schedule, and demonstration of biologic activity as proof-of-principle. Biologic activity will be defined as any immunological effect induced by the vaccine on the target disease or host immune system using biologic markers as study end points, for example, clinical, molecular, or immune response. If proof-of-principle trials demonstrate an immune response, or other biologic or clinical activity, efficacy trials may be initiated. Efficacy trials formally establish clinical benefit either directly or through a surrogate and are encouraged to be randomized studies. Efficacy trials may use prospectively planned adaptive designs to expand from randomized phase 2 into phase 3 studies if well-defined trigger-point criteria are met, but the cost of incorporating such design elements should be carefully evaluated.

Answers to specific questions should be considered possible area of research in the following years: Should all cancer patients be treated with an active immunotherapy approach or only individuals potentially more "responding"? How can we predict that the individual will develop an immune response against a particular antigen used in the vaccine formulation? What are the risks associated with such a vaccination, i.e. the possibility to develop an autoimmune response? What is the durability of immune protection? Can we combine vaccine therapy with therapeutic monoclonal antibodies or small target oriented molecules?

There is no doubt that the findings reported in cancer prevention vaccination trials open a new field at the interface of basic science, clinical medicine, public health, and public policy. To improve the efficacy of the breast cancer vaccines we need a better understanding of the relation between innate and adaptive immune responses, and of the immune escape mechanisms employed by tumor cells, the discovery of mechanisms underlying immunological tolerance, and acknowledgment of the importance of both cell-mediated and humoral adaptive immunity for the control of tumor growth.

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S17 Breast cancer stem cells: Getting to treat the core

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There is increasing evidence that many cancers including breast cancer are driven by a cellular component that displays stem cell properties. These “cancer stem cells” may also mediate tumor metastasis and contribute to treatment resistance. In order to develop novel strategies to target these cell populations we have elucidated a number of signal transduction pathways which regulate the self-renewal and survival of breast cancer stem cells. These pathways include both cell autonomous and paracrine signaling from the cancer stem cell “niche.” Intrinsic signaling networks involving interactions between Notch, Hedgehog, and Wnt pathways, in addition the HER2-PTEN and AKT pathways regulate breast cancer stem cell self-renewal. The remarkable clinical efficacy of HER2 targeting agents such as trastuzumab may relate to their ability to target cancer stem cells.