

Management of Breast Cancer by Vaccine: Fact or Fiction

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Abstract

Breast cancer (BC) is the most common malignancy (75-80%) among women. Options for management of BC are multivariate. Available modalities include surgery, radiotherapy, chemotherapy and hormone therapy. Despite availability of improved therapeutic adjuncts, mortality from BC is 40%. Vaccination strategies against BC are emerging as a viable alternative. This review highlights the available results of this emerging therapeutic strategy.

Key words: Breast cancer, Vaccine

Breast cancer (BC) is the most common malignancy (75-80%) among women.¹ Options for management of BC are multivariate. Available modalities include surgery, radiotherapy, chemotherapy and hormone therapy. Despite availability of improved therapeutic adjuncts, 39,970 BC deaths were expected in 2011.² Vaccination strategies against BC are emerging as a viable alternative. Tumor immunology is one of the exploding fields in cancer research. Evidence of development of subtle degree of antitumor immunity by the host has been reported in literature³ This has encouraged in-vitro formulation of active and passive immunization strategies against cancer. Malignancies like cervical cancer have specific infective agents as their principal etiology and vaccination against them is relatively easy.⁴ But in other cancers, like BC, developing a vaccine depends on identifying

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appropriate tumor antigen. Groups of antigens are expressed in BC, often more than one in a single patient. The initial strategy of developing a vaccine based on a single antigen has thus failed to achieve clinical significance. Later vaccines targeting multiple antigens were investigated. Many of these were combined with chemotherapy and hormone therapy to get the best possible result. This review highlights the available results of this emerging therapeutic strategy.

Vaccination Strategies

Vaccines targeting different tumor antigens have been developed for clinical use. Some have definite antigenic targets. These function by manipulating B-cell, T-cell or antigen presenting cell (APC) activity. Some vaccines act by directly activating humoral immunity. A second modality of immunotherapy is passive immunization with preformed antibodies against tumor antigens.

Antigens

BC patients develop subtle degree of immunity

against certain antigens like MUC-1 and HER-2/neu. A variety of other antigens has been identified. These include Carcino Embryonic Antigen (CEA), p53, Sialyl -Tn (STn), melanoma-associated antigen (MAGE), GAGE, BAGE, XAGE and h TERT , alpha -lactalbumin.^{4,5,6,7,8,9}

Clinical Trials with BC Vaccines

HER-2/neu related vaccines

HER-2/neu is one of the most extensively tested vaccine targets. Vaccines act by targeting HER-2/neu extracellular and intracellular domains. The first clinical data on HER-2/ neu vaccine was published in 1999¹⁰ where anti HER 2/neu vaccine with was used in stage III, IV HER-2/ neu positive BC over six months. The aim was to detect CD4+ response. Ninety-two percent of the patients completing six vaccinations developed HER-2/neu immunity to at least one peptide component of the vaccine as measured by peptide-specific T-cell proliferation in vitro. Additionally development of immunity against some epitopes of HER-2/neu which were not delivered by vaccine and HER-2/neu specific delayed hypersensitivity was observed which indicated the activated T cell mediated localization of site of antigen deposition. This immunity persisted for at least one year in 38% of patients.

Further HLA- A2 restricted HER-2-derived peptide p369-377 given with GM-CSF adjuvant to patients with metastatic breast resulted in development of new peptide-specific delayed type hypersensitivity (DTH) and antigen-specific CTLs capable of lysing HER-2/neu expressing tumors.¹¹

Vaccines to stimulate HER2 intracellular domain (ICD)-specific T cell and antibody were administered intradermally/subcutaneously four times at 3-week intervals to patients with stage II, III, or IV breast cancer with more than 50% HER2 over-expressing tumor cells who were disease-free after surgery and adjuvant therapy.¹² ICD-specific

T cell and antibody responses were measured. Delayed-type hypersensitivity (DTH) reactions at the injection site and HER2 specificity was detected by cytokine flow cytometry in majority of the patients. At more than 5 years of follow-up, 86% (six out of seven) had detectable anti-ICD antibodies. One patient experienced a pulmonary recurrence at 4 years. Although this was a small pilot study, the well-tolerated nature of the vaccines, the lack of cardiac toxicity, significant immunogenicity, and a 100% 4.5-year survival rate suggest that vaccination with HER2 ICD is appropriate for further study.¹³

In US Military Cancer Institute Clinical Trials Group Study I-01 and I-02 E75, a HER-2/neu-derived peptide, was administered as a preventive vaccine with granulocyte-macrophage-colony-stimulating factor (GM-CSF) in disease-free lymph node-positive and lymph node-negative BC patients. The optimal biologic dose (OBD) was determined based on toxicity and immunologic response. Patients were vaccinated over 6 months (3, 4, or 6 times) with different doses of E75 plus GM-CSF. Immunologic response was measured by DTH and E75-specific CD8+ T-cells were quantified. Ninety-nine patients were vaccinated in 7 dose groups. Results revealed a trend toward an increase in the average postvaccine dimer, a significantly larger DTH response and a trend toward decreased recurrences for larger tumors, more positive lymph nodes and high grade tumors with a median follow-up time of one and a half years.^{9,14}

Recently developed DNA vaccination is a viable alternative to peptide vaccination to induce potent anti-tumor CD8 T cell responses that provide effective therapeutic benefit.¹⁵

Studies to evaluate the early immunotherapeutic targeting of HER-2/neu in ductal carcinoma in situ DCIS revealed encouraging results.¹⁵ Preoperative HER-2/neu positive DCIS patients, vaccinations of dendritic

cells pulsed with HER-2/neu HLA class I and II peptides were done at four weekly intervals. Sixty-three per cent of the patients showed markedly decreased HER-2/neu expression in surgical tumor specimens, often with measurable decreases in residual DCIS, suggesting an active process of "immunoediting" for HER-2/neu-expressing tumor cells following vaccination. Vaccination strategies may therefore have potential for both the prevention and the treatment of early breast cancer.

MUC1 related vaccines

MUC1 is another widely investigated antigen in BC. Peptide or carbohydrate based vaccines have been developed. MUC1 remains mostly in unglycosylated form in cancer, and thus the antigens on the cancer surface are different from normal cell.¹⁶ Therefore targeting MUC1 for cancer immunotherapy can exploit the difference between cancer and normal cells, eliminating the cancerous cells while leaving the normal mammary cells unharmed. Preclinical trials with MUC1 showed that MUC1 is a relatively poor immunogen in humans. Anti-MUC1 tumor immunity has been initiated by vaccination of mice with the recombinant bacillus Calmette-Guérin-based breast cancer vaccine that co-expresses variable-number tandem repeats of MUC1 and CD80.¹⁷ Experimental studies using two recombinant bacillus Calmette-Guérin (BCG) vaccines (rBCG-MVNTR4-CSF and rBCG-MVNTR8-CSF) have shown encouraging results.¹⁸ Moreover, evaluation of N-terminal region (2-147 amino acids) of MUC1 (MUC1-N) for dendritic cell (DC)-based cancer immunotherapy has yielded good results.¹⁹ GM-CSF has been shown to increase the percentage and activity of antigen-presenting cells.²⁰ Post-translational modifications like phosphorylation and glycosylation of important functional motifs of MUC1 play an important role in presenting MUC1 as a candidate for breast

cancer vaccine.²¹ TG4010 vaccine, which incorporates the MUC1 antigen into a non-propagative pox viral vector, and interleukin-2 incorporated TG4010 as an immune stimulus have been tested in BC with encouraging results.²²

DNA plasmids encoding human MUC1 (pMUC1) and mouse interleukin-18 (pmuIL-18) has demonstrated effective results in preventing and treating pulmonary metastases in animal models.²³

CEA-related vaccines

Immunotherapy with these CEA cancer vaccines may prove most effective in the adjuvant setting, where disease has been controlled or stabilized with conventional therapies. The development of CEA cancer vaccines involves many parameters, including the appropriate form of the vaccine, i.e., recombinant protein, peptides, vectors etc., the use of classical adjuvants and/or biological adjuvants such as cytokines, and the use of T cell costimulatory molecules.²⁴

Poly Vaccine

Poly vaccine regimen consisting of the genes for CEA and MUC-1, along with co-stimulatory molecules (TRICOM; composed of B7.1, intercellular adhesion molecule 1, and lymphocyte function-associated antigen 3), is well tolerated and safe and has shown evidence of clinical activity.²⁵ It is associated with both CD8 and CD4 immune responses and has a 2% low grade injection-site reaction.

Alfa- Lactalbumin, the Novel Vaccine

Jaini from Cleveland clinic has worked on this new antigen, alpha-lactalbumin, as target vaccine autoantigen because it is a breast-specific differentiation protein expressed in high amounts in the majority of human breast carcinomas and in mammary epithelial cells only during lactation. This vaccine has experimentally proved to induce mammary gland failure during lactation and

tumorogenesis, thus preventing breast cancer. But the problems of this vaccine are lactation failure and the fact that not all the BC patients express alfa-lactalbumin.²⁶

Discussion

High mortality despite modern treatment modalities was the impetus for the search for alternative therapy. Immunotherapy came up as a viable modality. Passive immunization of BC patients with Trastuzumab has been used clinically with moderate results. Active immunization with vaccines targeting different tumor antigens is one of the exploitable fields in biotechnology. Different preclinical and clinical studies have reported a variety of results as discussed previously, but none showed gold standard results. The prime difficulty encountered during vaccine development was the continuous dynamic interaction between tumor cell and host immunity. Each modified the other. Thus experimentally successful vaccines did not show promising result in clinical studies. There is down-regulation of antigen when therapeutic antibody is used. This is known as "Antigen loss variant resistance."²⁵ This necessitates the formulation of vaccines targeting multiple antigens. Even these polyvalent vaccines developed resistance because of down-regulation of components of antigen processing pathway like MHC I/II, Transporter associated protein.²⁵ Furthermore, all the tumor antigens are recognized as self antigen by host immunity. Studies demonstrated that there is development of immune suppression in patients with BC.

Conclusion

Vaccination is a novel modality in breast cancer treatment. Studies have shown mixed results. Moreover, issues related to use of vaccine for prevention or treatment, determination of dosage and suitability as a primary or adjuvant

therapy are yet to be solved. Further studies are to be conducted to establish this as a prime therapy of BC. Data on ongoing trials on BC vaccine are available on National Cancer Institute (NCI) website.²⁶

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