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A Study of Clinical Development and Effectiveness for Breast Cancer Vaccine

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Abstract – The manipulation of the immune system through the administration of a vaccine to direct an effective and long-lasting immune response against breast cancer (BC) cells is an attractive strategy. Vaccines would have several theoretical advantages over standard therapies, including low toxicities, high specificity, and long-lasting efficacy due to the establishment of immunological memory. However, BC vaccines have failed to demonstrate meaningful results in clinical trials so far. This reflects the intrinsic difficulty in breaking the complex immune escaping mechanisms developed by cancer cells. New vaccines should be able to elicit complex immunologic response involving multiple immune effectors such as cytotoxic and antibody secreting B cells, innate immunity effectors, and memory cells. Moreover, especially in patients with large tumor burdens and metastatic disease, combining vaccines with other strategies, such as systemic BC therapies, passive immunotherapy, or immunomodulatory agents, could increase the effectiveness of each approach. Here, we review recent advances in BC vaccines, focusing on suitable targets and innovative strategies. We report results of most recent trials investigating active immunotherapy in BC and provide possible future perspectives in this field of research.

Keywords: Cancer Vaccines, Cancer Immunoprevention, Cancer Immunotherapy, Breast Cancer, etc.

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INTRODUCTION

Recently, advances in early diagnosis and more effective treatments have reduced the mortality rate due to breast cancer (BC). However, despite this progress, BC remains a leading cause of death in the female population worldwide. In this scenario, manipulating the immune system to direct an effective and long-term immune response against BC cells through the administration of a vaccine is an attractive strategy. Tumor vaccination would have several theoretical advantages over standard therapies. First, the ideal tumor vaccine would induce potent and durable immune reactions against a broad spectrum of tumor antigens. It could be easily administered and manufactured, with modest side effects typical of conventional chemotherapies. Moreover, it would prevent further tumor recurrences, due to the establishment of persistent immune memory (Kiewe & Thiel, 2008). At present, however, active immunotherapeutic strategies against cancer have failed to fulfill the above expectations in clinical trials. This reflects the intrinsic difficulty in finding optimal targets for a cancer vaccine, the most effective type of vaccination, route of administration, and the most immunologically favorable setting of disease (eg, low tumor burden, not heavily pretreated patients). Most importantly, it reflects the difficulty in breaking the complex immune-escaping mechanisms developed by cancer cells. The aim of this review is to summarize recent advances in BC active immunotherapy, to address recent results from clinical trials, and to provide possible future perspectives in this field of research.

In this context, immunotherapy has always been an attractive and potentially efficient treatment for cancer patients (Sica & Bronte, 2007). Tumor immunotherapy can generally be classified as (a) passive (or adaptive), consisting of administration of cells or antibodies ex vivo, and (b) active, represented by vaccines, aimed at eliciting a specific immune response against tumor-specific antigens (TSAs) and tumor-associated antigens (TAAs). Prophylactic and therapeutic vaccines represent one of the most intriguing approaches in the multidisciplinary treatment of cancer patients. Compared to all other standard modalities (surgery, chemotherapy, radiotherapy, and adaptive immunotherapy), an effective vaccine-based immune response against tumor may be the only cancer treatment with the potential to last a lifetime (Curiel, 2007). Theoretically, vaccinated patients could mount an immune response able to either cure tumor or keep it under constant restraint (i.e., immune surveillance), delaying tumor recurrence and prolonging survival.

One of the major problems in developing an efficient cancer vaccine is the lack of TSAs and the weakness

of immune responses against TAAs, usually recognized by the immune system as self-antigens. During the last decades, various strategies for therapeutic cancer vaccines have been proposed to overcome this weak immune response against TAAs, including cell-based vaccines, DNA- or RNA-based vaccines, protein- or peptide-based vaccines, and vector-based vaccines (Hodi, et. al., 2008). The common rationale for all these modalities is the activation of antigen-presenting cells (APCs) and the stimulation of an antigen-specific cytotoxic T lymphocyte-(CTL-) mediated immune response. Dendritic cells (DCs) are the most potent APCs, and various strategies have been used to enhance their ability to activate T cells. This review focuses on the state of the art of these modalities and analyzes the most promising phase II/III clinical trials, emphasizing vaccines directed against carcinomas. Despite recent achievements, one criticism of some of these clinical trials has been the lack of immunological data supporting the significant improvements in time to progression and overall survival (OS) observed. An effort should be made to define the specific components of each immune response as a consequence of anticancer vaccination. In this context, both the specificity and the identification of potential escape mechanisms (i.e., increase of Treg number or function, balance between positive and negative regulators of antitumor responses, such as CD28, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed death-1 molecule (PD-1) and its ligands PD-L1 and PD-L2) should be investigated. Increasing our understanding of how these modalities modulate the CTL response is vital to developing novel and effective antitumor vaccines.

The goal of therapeutic cancer vaccines is to “teach” the patient’s own immune system to specifically recognize and eliminate tumor cells. The potential target for the immune response can be either TSAs (antigens present only on tumor cells) or TAAs (antigens present mostly on tumor cells but also on some normal cells). Theoretically, TSAs are the ideal target for cancer immunotherapy because of their specificity (Hodi, et. al., 2008). They are largely composed of mutant proteins caused by somatic mutations in the original sequence of the protein. A major advantage of targeting TSAs is that many of these proteins have been demonstrated to be essential for tumorigenesis and cancer progression. On the other hand, a major drawback of targeting TSAs is the fact that most of the mutations identified are unique to each tumor, potentially requiring the development of personalized immunotherapy for individual patients. In contrast, TAAs are commonly expressed on tumors with the same histology and are shared among tumors of different origin (Stagg, et. al., 2008). A major limitation of targeting TAAs is that they are weakly immunogenic due to the tolerance for self-antigens acquired by the immune system in its developmental stages.

In the last decades, several different mechanisms have been proposed to “instruct” DCs, the most potent APCs known, to induce Th and CTL responses against tumor antigens, thus breaking immune tolerance. Antigen-loading techniques include (a) infecting DCs with viral, bacterial, or yeast vectors, (b) pulsing DCs with proteins or peptides, (c) loading DCs with tumor cells or tumor-cell lysates, and (d) transfecting DCs with DNA or RNA

Encouraged by positive preclinical and clinical data, further studies are currently ongoing to evaluate the possibility to enhance vaccine-induced immunity by combining vaccines with low doses of chemotherapeutic agents (i.e., cyclophosphamide, doxorubicin, docetaxel) or radiation therapy, that showed synergistic immunotherapeutic effects when given in proper sequence.

REVIEW OF LITERATURE:

India is a developing country with diverse population groups following variable lifestyles and dietary habits in the world. The incidence of breast cancer in India is significantly lower, almost one quarter to one-third of that in North America and Europe, respectively. This is primarily because of virtually nonexistent breast cancer screening programs, lack of awareness and socio-cultural attitudes (Takeda, et. al., 2007), in some states of the country.

Reports from national cancer registries reveal breast cancer as the commonest cancer amongst women in major metropolitan cities of India with projected breast cancer cases in India to surpass cervical cancer in the year 2020. This increasing rate of Breast cancer in India demands for a quick study of the disease and search for markers and effective therapy.

The breast is internally composed of the following parts:

- **Lobes and Lobules**

Lobules are small milk ducts comprising 10-100 alveoli. Cluster of 20-40 lobules forms the lobes. 15-25 lobes together make the mammary gland. These lobes radiate around the nipple.

- **Glandular tissue**

Glandular tissues are responsible for milk production and transportation which is composed of:

- Alveoli – These are the epithelial grape-like cluster of cells which produce milk.
- Ductules – These are the branch-like tubules extending from the clusters of alveoli and empty into larger lactiferous ducts.

- Lactiferous ducts – These ducts widen underneath the areola and nipple to become lactiferous sinuses.

- Lactiferous sinuses – They perform the job of collecting milk from the lactiferous ducts into the nipple pore.

- **Connective tissue**

Connective tissue supports the breast. The ligaments named "Cooper's ligaments" which are fibrous bands attach the breast to the chest wall and avoid the breast from sagging.

- Blood as a connective tissue nourishes breast and supplies the nutrients needed for milk production.

- Nerves provide sensitivity to touch and stimulate the release of hormones while baby's suck which triggers the milk ejection reflex, stimulated by oxytocin and the production of milk by prolactin harmone.

- Lymph nodes perform the function of removing waste products.

- Adipose tissue (fat) allows protection to the tissue from injury.

The breast is externally composed of the following parts:

- Areola is the pigmented area at the center of each breast.

- Nipple protrudes at the center of each breast.

The function of producing milk is regulated by hormones. Stimulation of the female sex hormone, estrogen, causes the development of glandular tissue in the female breast during puberty. Increase estrogen levels during pregnancy causes the breast size to increase in size through the accumulation of adipose tissues. Presence of progesterone stimulates the growth and maturation of the duct system. During pregnancy levels of estrogen and progesterone rises (levels are needed to sustain pregnancy) that further enhances the development of the mammary glands.

This is the main reason why pregnant women has larger and more enhanced breast. Another hormone important for the implementation of mammary gland function is the presence of prolactin and oxytocin. Without these hormones, milk will not be produced and ejected out of the breast. Prolactin from the anterior pituitary gland stimulates the production of milk in the glandular tissues while oxytocin causes the ejection of milk from the glands. Breast cancer is a cancer that starts in the tissues of the breast. There are two major types of breast cancer: Ductal carcinoma starts in the tubes (ducts) that move milk from the breast to the nipple (NON-Invasive form is known as DCIS) and Lobular carcinoma starts in the parts of the breast, called lobules, that produce milk. (NON-Invasive form is known as LCIS).

In rare cases, breast cancer can start in other areas of the breast. The risk factors for breast cancer include: age, family history, genes, menstrual cycle, excessive alcohol use, radiation and hormone therapy. The major symptoms are: Breast lump or lump in the armpit that is hard, has uneven edges, and usually does not hurt Change in the size, shape, or feel of the breast or nipple, fluid coming from the nipple -- may be bloody, clear to yellow, green, and look like pus bone pain, breast pain or discomfort, skin ulcers, swelling of one arm (next to the breast with cancer) and weight loss.

Regulatory Framework for Development of Cancer Vaccines: To date, an estimated more than 10,000 people have participated in late-stage clinical trials of active cancer immunotherapies. The vast majority of these studies have failed to demonstrate any meaningful efficacy with a large proportion of unsuccessful phase III studies conducted with vaccine candidates that looked quite good in early trials. Significant investment and development efforts made by industry and academia resulted in a considerable number of IND submissions and scientific advice interactions between developers and regulatory agencies in the past 20 years. The objective of this review is to provide an overview of most up-to-date regulatory considerations relevant to cancer vaccine products in EU, US, Japan, and some emerging markets.

European Regulatory System : In 1995–2011 y EMA has provided 2553 scientific advice (SA) and protocol assistance procedures across all classes of medicines with 26% of those falling into area of anti-neoplastic and immunomodulatory therapies. Between 2006–2011 EMA and FDA also assisted with 17 joint SA and protocol assistance procedures. In EMA and National authorities SA procedures on cancer vaccine products are driven by oncology experts based at national competent authorities and to a lesser extent by some external experts and advisory boards. Therapeutic cancer vaccines are not subject of consideration by EMA Vaccine Working Party that is focused on preventative vaccines for infectious and communicable diseases. Due to complex and heterogeneous nature of some cancer immunotherapeutic, cell-, virus- and gene therapy-based products might be scrutinized by Committee of Advanced Therapies (CAT) and Gene therapy Working Party functioning within CAT. The quality issues arising on cancer vaccines submitted for full

marketing authorization application (MAA) in the EU or products under SA assistance may also be taken for discussions at EMA Biologics Working Party. Coordination of all administrative issues pertaining to SA, including allocation of coordinators and peer-reviewers, requesting the input from different working parties and experts, issuing SA letters etc. is handled by EMA Scientific Advice Working Party (SAWP). Committee of Human Proprietary Medicinal products (CHMP), SAWP, Oncology Working Party and CHMP Scientific Advisory Group on Oncology may independently or jointly recommend on specific needs for further EU guidelines in relation to development of oncology products and specifically cancer immunotherapies. The need for guidelines is dependent on the demand for SA around specific therapeutic areas and EMA experience with evaluation of novel agents. For example, if there are major disagreements between applicants and EMA as well as discordance of views on the scope of the data requirements arising between Rapporteurs and assessors from national agencies, then consideration is given to the development of a guideline that provides the industry and assessors with harmonized framework for clinical data evaluation (Pañares & Garcia, 2007). Prior such guideline is developed and issued it is preferred to obtain a "real-life" experience with evaluating one or two products coming through MAA submission. In recent years EMA has experienced several MAA submissions related to cancer immunotherapies (Morse, et. al., 2010). There is also currently ongoing EMA submission of Provenge in castrate-resistant prostate cancer which is under evaluation.

FDA Requirements on Cancer Vaccines : FDA reported that in 2010 in excess of 1400 active investigational files were handled by FDA Offices and Departments. Oncology drug developers are increasingly required to consider use of different biomarkers in development of targeted therapies. FDA Critical Path initiative which was launched in 2004 has proposed this paradigm but, according to a 2008 review, only 3% of clinical trials have incorporated a novel biomarker of efficacy into their clinical trial design and there are significant delays with development of diagnostic companion tests. FDA has kept a considerable interest to cancer immunotherapies through participation in numerous workshops and conferences, e.g., FDA/NCI Co-Sponsored Workshop on Cancer Vaccines and Immunotherapy in 2007 and 2nd World Cancer Vaccine Congress in Boston in 2011 and other events. From FDA perspective, cancer vaccines fall into category of products evaluated by Office of Cellular, Tissue and Gene Therapy products at CBER (Center for Biologics Evaluation and Research). Immunotherapy products that include adjuvants, nanoparticles and other non-cell derived components may require involvement of CDER (Center of Drug Evaluation and Research), CDRH (Center for Devices and Radiological Health), Office of Combination products (OCP) and Office of Drug Safety (ODS). Combination of cancer vaccines with other agents into single formulation poses particular challenges for developers as CMC data may reside in Master Files or cross-referenced files may not be accessible to applicants. In addition, FDA cannot discuss or divulge CMC issues without holder's authorization. Therefore it is crucial that applicants seek a comprehensive and transparent exchange of the data on in-licensed components from licensor's CMC files.

For the approval of a Biologics License Application (BLA), it is critical that sufficient evidence of effectiveness is available so that both the sponsor and the FDA can adequately complete the benefit/risk (B/R) assessment of the new molecular entity (NME) (21CFR 314.126). In addition, the product should be of acceptable safety [10] and the product label would define an appropriate patient population and provide with an adequate information enabling safe and effective use of the product 21CFR 201). Section 505(d) of the FD&C Act, as well as Section 351 of the Public Health Service Act, indicate that new drugs and biologics should establish substantial evidence of clinical effectiveness through means of "adequate and well-controlled studies." The base assumption is that since the term *studies* is plural, two or more controlled randomized clinical trials are required to establish efficacy. Specifically in oncology, there are many scenarios (and many past examples) where FDA rendered a single pivotal study sufficient for approval. The case for adequacy of a single study as well as a qualification for accelerated evaluation and approval should be made on the basis of advantages seen with the product in extending PFS and OS (as per phase I–III studies), gains observed in evaluation of patient-reported outcomes and quality of life; and favorable effect on established surrogate and composite endpoints. With potential limitations and caveats in clinical data, sponsors might be prepared to seek a conditional approval route with ways to generate further clinical data supporting clinical benefits via post-approval commitments.

DNA and RNA Vaccines: DNA-based vaccines are a recently developed strategy that has proven capable of activating strong immunity against weak TAAs. Several approaches have been developed and evaluated for enhancing the potency of DNA-based vaccines, including improved delivery systems (Gene Gun, cationic liposomes) simultaneous administration of cytokines (GM-CSF or IL2) and the use of separate plasmids encoding non self-antigens (i.e., hepatitis B surface antigen). The immunogenicity of DNA-based vaccines can also be enhanced by various modifications of plasmid-encoded antigens.

Recently, several phase I/II clinical trials employing DNA-based vaccines targeting different TAAs (i.e., PSA, PAP, gp100, CEA, hsp65) have been conducted in patients with prostate cancer, melanoma, colorectal cancer, and head and neck

carcinomas. In all these trials, DNA-based vaccines were administered either as monotherapy or in association with different delivery systems and adjuvants. In terms of immune response, most of these trials showed a low immunogenicity of TAAs. The small sample size of these phase I/II studies precludes achieving a statistical correlation between development of an immune response and clinical outcomes in vaccinated patients (Coveler, et. al., 2009). Evidence of clinical benefit must be evaluated in larger studies.

MRNA-based gene transfer vaccines are another attractive immunotherapeutic approach to cancer treatment. This method, based primarily on transient transfection of no dividing cells, is regarded as pharmaceutically safe because the transfected mRNA does not integrate into the host genome. In addition, high transfection efficiency can be achieved by electroporation. mRNA, which can be effectively overexpressed in target cells, is generated by in vitro transcription from a bacteriophage promoter-equipped plasmid DNA. It is composed of a cap structure at the end, the coding RNA for target antigen, and a tail of poly-adenosine (poly A tail). The target antigen used can be a single peptide PSA or CEA, allogeneic cancer cell lines, or autologous tumor mRNA. The mRNA-based vaccine containing the mRNA-coding TAA is transfected into DCs and translated into proteins. After protein processing, the antigen can be loaded on MHC molecules for antigen presentation, thus activating an antigen-specific CTL response.

Path for Development of Cancer Vaccines: The technologies for cancer vaccination have been extensively reviewed elsewhere. In brief, therapeutic cancer vaccines can be off-shelf available (recombinant antigen cocktails, recombinant microorganisms, whole tumor cell derived (allogeneic), oncolytic viruses, anti-idiotypic antibodies, DNA and gene therapy based products) which could be manufactured and distributed worldwide and personalized cancer vaccines (autologous cells and antigens, adoptive cell transfer) which are heavily dependent on specialized centers of expertise and manufacturing. Despite extensive prior efforts and trials, only one vaccine: Dendreon's Provenge (sipuleucel-T), a dendritic cell for metastatic castration-resistant prostate cancer, in so far has achieved an approval with FDA in 2010. In clinical development, sipuleucel-T was manufactured from autologous APC-containing peripheral blood mononuclear cells (PBMCs) of prostate cancer patients. PBMCs were obtained from a leukapheresis procedure. These cells were co-cultured with PA2024, the recombinant fusion protein of human PAP-GM-CSF, prior to reinfusion. Of note, sipuleucel-T comprises multiple types of mononuclear cells including APCs, CD4 and CD8 T cells, NK cells, and B cells. Provenge provides with approximately 4.1 mos in median OS improvement and has been introduced on US market at hefty $93,000 per treatment course for a regimen (three infusions given over one month). Significant company investment was required to overcome not only considerable development costs but also to solve various logistical hurdles with launching numerous FDA-certified centers across the US for production of Provenge. Crowded space of prostate cancer treatments along with pricing and logistical issues have created significant barriers for Provenge access across the US. Furthermore, high pricing and logistical barriers in expanding the supply chain makes significantly reduces probability of commercial success for the product in the EU, Japan and emerging markets.

Clinical Positioning and Treatment Paradigm: The ultimate outcome of the clinical development for a novel product is positioning in a subset of patients in whom the benefit-risk ratio is most favorable and most of target product profile features are well linked with anticipated clinical values and benefits (Disis, et. al., 2009). Any developers should be thinking about a specific market niche in context of crowded and competitive treatment paradigm, efficacy and safety attributes emerging from ongoing clinical studies and biomarkers or companion diagnostic tests predictive of the optimal clinical response. The market for prostate, breast and kidney cancer drugs has grown increasingly crowded in recent years with multiple agents in clinical development and several products approved across US, EU and Japan markets. For example, the old paradigm of renal cancer treatment was based on use of immunomodulatory therapy which provided a modest survival benefit, at the expense of considerable toxicity. Since 2005, seven targeted agents, bevacizumab, sorafenib, sunitinib, pazopanib, temsirolimus, everolimus and axitinib have been approved by the US FDA for the treatment of different lines of metastatic or locally invasive disease. In general, these agents have higher efficacy against clear cell than non-clear cell histologies. Similarly, the treatment paradigm for prostate and breast cancer has become incredibly competitive providing with only limited remaining opportunities and creating a fierce rivalry for immunotherapy products. By the time Provenge came into US market in 2010, the landscape for treating castrate-resistant prostate cancer has become very crowded. Two new agents: Sanofi's new chemotherapy Jevtana (cabazitaxel) and J&J's hormone therapy Zytiga (abiraterone) were approved by EMA and FDA in 2011 for patients following chemotherapy and is being positioned for earlier-stage patients after failure of primary androgen deprivation therapy and prior to chemotherapy, which is the same population targeted by Provenge. In addition, generic oral ketoconazole has a similar mechanism of action as abiraterone and, among other options, has been used for many years as a as

a second-line hormonal treatment prior to chemotherapy. US National Comprehensive Cancer Network guidelines include adrenal/paracrine androgen synthesis inhibitors abiraterone and ketoconazole as options for patients after initial castration therapy has failed. The guidelines specify that abiraterone may be used for metastatic CRPC patients who have not received prior chemotherapy, though it isn't the standard of care. Many other treatments are in development for prostate cancer and have shown promise leaving a scope for differentiation either for further improvements in safety/tolerability profile or provide with cost-effectiveness benefits for payers and health care.

CONCLUSION:

In recent years, outstanding progress has been achieved toward the cure of BC. More personalized therapies, molecularly targeted drugs, and a deeper understanding of the mechanisms of disease have allowed improving the prognosis of certain subtypes of tumor. In this rapidly changing scenario, there is a growing interest in developing an effective cancer vaccine. Unfortunately, none of the vaccine tested so far in clinical trials has turned out to be "practice changing." Nevertheless, three important lessons can be drawn. First, many vaccines elicit a measurable immunologic response, such as specific antibodies or specific CD8+ T-cells, but this response often has little or no impact on tumor growth. Engaging only one compartment of the immune system (eg, only cytotoxic response or humoral response) is probably not sufficient for an effective therapeutic vaccine. New vaccination strategies should therefore aim at eliciting a wide response, involving multiple immune effectors such as cytotoxic and antibody-secreting B-cells, innate immunity effectors, and memory cells. The underlying concept would be that a "complete" immunologic response may promote increased release of tumor cell fragments/antigens and proinflammatory cytokines, resulting in an immunologic virtuous cycle. Second, the main barrier against vaccination is probably due to complex immuno-escaping mechanisms developed by cancer cells. Regulatory cells such as T-Regs and molecular immune checkpoints (eg, CTLA-4, PD1/PD1L) play crucial roles in maintaining self-tolerance, and tumors are able to exploit these elements to get protection from immune system's attack. New strategies based on blocking antibodies, recombinant forms of ligands, or receptors should be implemented to block such modulatory checkpoints and strengthen the immune response, with promising initial translation into clinical setting. One of the most intriguing perspectives of these strategies is obviously their synergism with immunotherapy approaches such as cancer vaccines.

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