

Therapeutic Vaccines in Breast Cancer

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Abstract. Breast cancer (BC) is a major worldwide health issue, characterised by an increasing occurrence in both males and females. The classification of breast cancer subgroups is determined by variations in hormone receptor expression. Although traditional breast cancer therapies, including chemotherapy, surgery, and radiotherapy, have demonstrated effectiveness in the treatment of patients, they are frequently associated with significant adverse effects and recurrence. The emergence of therapeutic vaccines has become a promising option for the field of immunotherapy. These vaccines enhance the body's immune system to identify and eliminate cancerous tumour cells. The current approach to vaccine therapy for breast cancer focuses on the targeting of two main categories of antigens: tumour associated antigens and tumour specific antigens. Excitingly, multiple vaccine strategies for breast cancer treatment have been employed, all of which have demonstrated promise and effectiveness in clinical studies. Currently, proposed vaccine types include peptide-based vaccines, whole tumour cell vaccines, DNA/RNA-based vaccines, dendritic cell vaccines, and viral-vector vaccines, etc. This review examined the present state of different types of vaccines in breast cancer therapy, including the therapeutic mechanism and the treatment outcomes.

Keywords: Breast cancer; Therapeutic Vaccine; Immunotherapy.

1. Introduction

Breast cancer (BC), which accounts for 12.5% of global cancer incidence, has become the most frequently diagnosed cancer in both genders [1]. BC primarily affects women aged 50 and older, with the risk rising with age. Based on statistical data provided by the World Health Organization (WHO), it is estimated that around 2.3 million women were diagnosed with breast cancer in the year 2020, leading to a global mortality rate of 685,000. Breast cancer can be categorised into three primary subtypes, each characterised by the presence of unique hormone receptors [2]. The oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) are among the most widely recognized receptors [3]. Triple-negative breast cancer (TNBC) is a distinct subtype of breast cancer that is distinguished by the absence of three specific receptors on the surface of cancer cells.

The current therapeutic strategies for BC mainly include chemotherapy, surgery, and radiotherapy. Chemotherapy is a therapeutic approach that involves the use of cytotoxic medications with the aim of inhibiting or decelerating the development of cancerous cells. However, the efficacy of chemotherapy is compromised by its notable side effects and the development of treatment-resistant cancer cells. Radiotherapy, which is frequently used in combination with chemotherapy, involves the application of high-energy radiation to the whole or a portion of the breast tissue. Nevertheless, radiotherapy has the potential to induce cardiotoxicity and give rise to the development of resistance as well. Conventional surgical techniques encompass two options: mastectomy, which involves the complete removal of the breast, or lumpectomy, a procedure to excise the cancerous area from the breast. Unfortunately, both surgical approaches are associated with drawbacks such as cosmetic dissatisfaction and the potential for recurrence [4]. Therefore, it is necessary to investigate novel treatment strategies in order to attain more effective treatment and reduce potential side effects.

Immunotherapy is a method of treating cancer that uses biological substances either synthesised inside the body or in the laboratory to enhance the body's immune response. By doing this, it boosts the body's ability to target and destroy cancerous cells. Employing therapeutic vaccines for the treatment and prevention of cancer is one of the subfields of immunotherapy. In recent years, therapeutic vaccines have represented a promising development in the treatment of BC.

Immunotherapy has brought about a revolutionary shift in BC therapy. The immune system can be activated to enhance the detection and eradication of cancer cells through the introduction of tumour-associated antigens (TAAs) and tumour-specific antigens (TSAs) [5]. The potential of these vaccines lies in their ability to overcome some limitations associated with traditional therapies, as they function by directing the immune system to recognize and eradicate breast cancer cells. This enabled the body's adaptive immune response to effectively reduce the risk of recurrence and limit the adverse effects of conventional treatment. In addition, therapeutic vaccines provide the opportunity to tailor treatment to individual patients by focusing on distinct subtypes of BC, thereby increasing therapeutic efficacy across a diverse population.

Therapeutic vaccinations now available can be categorised into two primary classifications: vaccines that target tumour-associated antigens (TAAs) and vaccines that target tumour-specific antigens (TSAs). They can be delivered through different platforms to induce antitumor immune responses. Existing delivery systems include vaccines based on whole tumour cells, dendritic cell vaccines, peptide-based vaccines, and DNA/RNA vaccines, etc. [1, 5].

In this review, I briefly introduced the basis of breast cancer and the significance of developing innovative therapeutic treatment methods. The introduction of different vaccine delivery platforms and the current state of clinical trials of different types of vaccines will also be discussed in further detail.

2. Types of Therapeutic Vaccines

2.1. Whole Tumour Cell Vaccines

The whole tumour cell vaccine involves deriving cancer cells from autologous (individual's own cell) or allogeneic (laboratory-grown cell) tumours [1, 6]. The antigen present in the cancerous cells includes epitopes recognised by the CD4⁺ and CD8⁺ T-cells, inducing a strong T-cell response [7]. The main advantage of this approach is that the tumour cell obtained already contains all potential antigens inside, thus eliminating the need to identify the most immunogenetic antigen for every individual. Moreover, by using a whole tumour cell vaccine, more than one antigen can be targeted at once, inducing multiple immune responses and reducing the possibility of tumour antigen loss. One limitation of such an approach is the difficulty in technically harnessing sufficient quantity of tumour cells that contain a certain number of cytokines. This makes the process both time- and money-consuming [8]. Due to the lack of effective treatment methods for late-stage BC, allogeneic whole tumour cell vaccines serve as a potential adjuvant option for chemotherapy and are investigated in clinical trials. The investigated vaccine contains genetically modified cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), which are shown to be safe and clinically effective during phase I and II clinical trials. Specifically, in a phase I clinical trial, the efficacy of the vaccine is being evaluated in 28 patients with metastatic BC. The results show that patients are well tolerated in using up to 4 doses of the vaccine with the minimum level of toxicity. A low dose of chemotherapy accompanied by a vaccine can be used to break such tolerance and sustain the T-cell driven HER2-specific immunity induced by the vaccine alone. Nevertheless, the immunological response elicited alone by the vaccine remains insufficient to overcome immune suppression caused by the tumour cell; therefore, it cannot be used effectively as a monotherapy [9].

2.2. Peptide-based Vaccines

A histocompatibility complex (MHC) class I restricted peptide epitope is introduced into the human host as the basic working principle of peptide-based vaccinations in order to trigger an immune response towards TAAs or TSAs. Antigen-presenting cells (APCs) are responsible for the recognition and processing of peptides. Once identified, these peptides are subsequently delivered to immune effector cells, which in turn activate the host immune response to eliminate tumor cells that possess the corresponding antigen. Peptide-based vaccines are relatively easier and cheaper to synthesize, and are relatively stable when transported, making large-scale production and delivery more achievable

[10]. Moreover, the limited and tolerable side effects make peptide-based vaccines safer when used in the treatment of BC. The limited diversity of human leukocyte antigen (HLA) subtypes in individual peptides is the most significant constraint of this treatment method. Individuals lacking expression of human leukocyte antigen (HLA) are not able to be injected with this particular vaccination, hence heightening the probability of insufficient immunogenicity. Moreover, it is noteworthy to mention that the capacity of MHC class I binding peptides to elicit activation of helper T-cells is often restricted, resulting in a reduced capability to activate CD8⁺ cytotoxic T cells. This phenomenon leads to either a restricted or temporary immunological response [11]. A clinical phase I/II study investigated a peptide-based vaccine involving peptides extracted from 3 types of TAAs from patients with BC. The results show a high CD8⁺ response and production of IFN- γ to at least one type of antigen. The low toxicity also suggests the high safety of the vaccine. The only peptide-based vaccine in clinical phase III is NewVaxTM, which involves the combination of peptide E75 and GM-CSF. The result shows that the vaccine is safe to use and has high efficacy. Additionally, the study has demonstrated that the intervention effectively reduces the recurrence rate by up to 50% in persons who possess an elevated risk of developing breast cancer [12].

2.3. Dendritic Cell Vaccines

Antigen-presenting cells (APCs), particularly dendritic cells (DCs), possess the capacity to undergo antigen processing and subsequently transmit antigens to both CD4⁺ helper T-cells and CD8⁺ cytotoxic T-cells. Dendritic cells have the ability to begin humoral immunity, hence triggering the following activation of natural killer (NK) cells and natural killer T (NK-T) cells. Dendritic cells that are produced ex vivo, frequently combined with peptides or transfected with viral designs, can be used as a cancer vaccine candidate [13]. The advantages of this type of vaccine is that it can enhance or bypass convectional antigen-presenting pathways. This induces a highly targeted and potent immune response. The disadvantages of such a delivery platform are that the manufacturing process is long and both time- and money-consuming [1]. Despite encountering such challenges, a number of clinical trials involving the dendritic cell vaccine have been conducted. A total of 20 patients diagnosed with BC were enrolled in a phase I/II clinical trial with the objective of evaluating the safety and effectiveness of autologous antigen-free dendritic cells (DC) and N-acetylcysteine-activated autologous cytotoxic T lymphocytes (NAC-AC) vaccines. The result suggests that autologous DC treatment accompanied by chemotherapy can effectively restore T cell activity and is safe to use in patients [14]. This makes the dendritic cell vaccine a potential vaccine for treating BC patients.

2.4. DNA/RNA-based Vaccines

A DNA-based vaccine involves delivering the sequence of genetic information that codes for the tumour antigen into the host body. Due to their ease of manufacturing and stability, DNA vaccines are regarded as the most practically feasible vaccination for the treatment of BC. The strand of DNA is encapsulated inside a delivery vehicle, usually in the form of plasmids or vectors. When the encapsulated DNA enters the host body, APCs take it up and translate it into cancer antigens, which triggers an antigen-specific immune response [15]. Despite the fact that DNA vaccines are easy to store and manufacture on a large scale, they possess fairly low immunogenicity due to a low rate of plasmid intake and ineffective antigen expression [3, 6]. Methods to overcome such drawbacks are taken, including approaches to making the vaccine replicate itself [16]. The predominant focus of scientific investigation pertaining to DNA/RNA vaccines for breast cancer involves the targeting of tumor-associated antigens (TAAs), including mammaglobin-A (MAM-A) and HER2/neu. No discernible T cell response was elicited in the initial clinical study of HER2/neu injection with modest doses of GM-CSF and interleukin-2 (IL-2). However, in a more recent phase I clinical trial on the HER2/neu DNA vaccine, the results were promising in both efficacy and tolerability. In another phase I trial, the MAM-A vaccine achieved success in eliciting a MAM-A specific CD8⁺ cytotoxic T-cell response. Progression-free survival (PFS) of BC patients has also been shown to be decreasing,

although the number of samples is limited. RNA vaccines share structural similarities with DNA vaccines and possess similar mechanisms as DNA vaccines, but they are specifically designed to target the host cell's cytoplasm. Therefore, it minimized certain safety considerations associated with the interaction between the genomes of the host cell. However, in contrast to DNA vaccines, RNA vaccines exhibit a notable degree of instability, hence posing challenges in terms of their delivery mechanisms, particularly with respect to lipid nanoparticles (LNPs) and liposomes. While viral vectors have the potential to transport RNA strands into the host body, the efficacy of antibody synthesis is reduced by this particular delivery mechanism [1, 17]. The main RNA type used in recent RNA vaccine therapy is the mRNA vaccine, which has been proven to be highly successful in targeting the COVID-19 virus. A recently initiated phase I clinical trial on RNA immunotherapy in the treatment of TNBC aims to investigate the tolerance and safety, as well as the T lymphocyte response, of the combination of two types of RNA immunotherapy. The findings indicate that all participants in the analysis generated CD4+ or CD8+ T cell responses to neoepitopes ranging from 1 to 10. This information suggests that in post-adjuvant TNBC patients, the method demonstrated a high level of efficacy in inducing strong and diverse T-cell responses targeting several epitopes.

2.5. Viral Vector-based Vaccines

Many viruses are inherently immunogenic. Consequently, it is possible to manipulate them in order to transport and manifest transgenes encoding tumor antigens within the host organism [18]. The modified viral vectors selectively target antigen-presenting cells (APCs), specifically dendritic cells, in order to initiate a tumour self-antigen specific immune response. By using viral vectors as a vehicle, the presentation of tumour antigens by APCs is enhanced, leading to a more active CD8+ cytotoxic T cell response. The immunogenicity of transgenes expressed in viral vector-based vaccines is therefore stronger than the administration of antigen with adjuvant, as shown in several studies previously. However, there are drawbacks to this delivery system. In some vectors, the host cell may induce neutralizing antibodies to the viral vector itself rather than to the transgene carried in it. This limits continual usage of vectors [19]. Numerous clinical trials have been done on the efficacy of viral vector vaccines in treating BC. The primary aim of ongoing phase II clinical research is to assess the immunogenicity of alphavirus-like replicon particles (VRPs) that encompass self-amplifying replicon RNA encoding for HER2. This will be achieved by assessing the levels of tumor-infiltrating lymphocytes (TILs) and anti-HER2 antibodies. The study is still ongoing, and the primary completion date is estimated to be December of 2023. Another phase 1b clinical trial aimed at investigating the efficacy of several viral vector-based vaccinations in a group of patients diagnosed with either HER2-positive BC or TNBCs. Regrettably, the trial consisted of only a single enrolled patient, resulting in an inability to carry out all intended research as originally outlined [20].

3. Conclusion

Significant advancements have been made in the creation of therapeutic BC vaccines in recent years. More and more promising vaccines are developed and examined in clinical trials. Several investigations done on the whole tumour cell vaccine have shown it to be effective and tolerable, though the efficacy is insufficient without being accompanied by chemotherapy. Peptide-based vaccine clinical trials have also shown high feasibility and effectiveness in lowering the recurrence rate in high-risk patients with BC. Similarly, to the whole tumour cell vaccine, with the dendritic cell vaccine, restoration of T cell activity can be shown in participants along with the use of chemotherapy. Being the most promising vaccine for the future, DNA/RNA vaccines for BC have shown high efficacy in inducing CD8+ cytotoxic T cell responses and reducing PFS in BC patients, though only a few samples are being tested. Viral vector vaccines are newly developed vaccines, and there are limited results in efficacy and safety upon usage. However, studies have shown viral vector vaccines to be more effective than antigens combined with adjuvants, providing a future path for therapeutic vaccines for BC.

While therapeutic breast cancer vaccines hold great promise, several challenges and opportunities for future research must be addressed. One key challenge is optimizing the efficacy of current vaccine platforms. Some vaccinations, including those based on peptides and dendritic cells, have shown promise but may require further refinement to enhance their effectiveness, particularly in patients with specific HLA subtypes. Additionally, improving the immunogenicity of DNA and RNA-based vaccines and overcoming host immune responses to viral vector-based vaccines are areas that demand attention. Also, assessing the tolerance and safety of therapeutic vaccinations, particularly when used in conjunction with other treatments like chemotherapy, is a problem. It is also fairly important to keep a balance between enhancing immune responses and minimizing adverse effects. As viral vector vaccine may be strong in efficacy, it is also concerned to have potential side effect. Furthermore, identifying the most appropriate vaccine platform for specific breast cancer subtypes is essential. Planning vaccine treatment for a specific patient is key to success in the treatment of cancer. Further research can focus on investigating suitable delivery vehicles and putting them into more clinical trials to prove their efficacy and safety.

The development of these vaccines can provide a new insight into the treatment of cancer by using the body's immune system to fight tumor cells. If a therapeutic vaccine can be put into clinical practice, it could potentially provide a cure for this incurable disease.

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