The efficacy of the therapeutic vaccine of breast cancer

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Abstract. Breast cancer (BC) is result of uncontrolled cell division of mammary epithelial cells that are affected by cancerogenic factors. In early phase, the symptoms always present as breast lumps, nipple discharge and axillary lymph lumps. For advanced BC, cancer cells are able to transfer to other organs, causing pathological changes all over the body that may be lethal to patients. According to the International Association of Cancer Registries from International Agency for Research on Cancer (IARC) in the year 2012, the morbidity of Europe is the highest, which reach 138.2/100,000, and Africa is the lowest, about 10.95/100,000. Except from Latin America, Asia and Africa, most of the regions have the morbidity over 130/100,000. As the investigation of WHO, the mortality of BC in 2020 is 29.8% globally, and over 99% cases are female patients. Without taking operation, chemotherapy, targeted treatment and endocrine therapy, therapeutic vaccine seems to be another treatment differ from other traditional treatment to cure breast cancer. Currently, chemotherapy, targeted therapy, and endocrine therapy have formed the cornerstone of non-surgical treatment of breast cancer, and the overall cure rate has also been significantly improved. However, current treatment methods do not have a good effect on patients with advanced breast cancer. Cancer vaccine therapy can use the specific anti-immune system of cancer cells to activate the immune system for a long time, especially because the body has a long-term immune memory, which can reduce the chance of cancer recurrence. This review introduces current therapies for BC and discusses potential vaccines for the treatment of BC.

Keywords: Breast cancer; vaccine; therapy.

1. Introduction

Breast cancer is one of the most common cancer over the world, while 2.26 million cases of female patients of breast cancer has been estimated in the year of 2020. Generally, less developed area is more likely to ill with breast cancer, however, the number of people who live in a under-standard environment are much more bigger than the people lived in developed countries [1]. Except from gender, aging is the most important factor that will cause the appearing of breast cancer. It was reported that roughly 99.3% patients were over the age of 40, and 71.2% were over the age of 60. In addition, heredity also has severe effect of getting breast cancer that a quarter of the cases have families who also has breast cancer [2]. Overall, radiation therapy, chemotherapy, endocrine therapy and systematic therapy, or even mastectomy are the main stream of breast cancer treatment, which have widely being used to cure multiple types of breast cancer caused by the pathological changes of different parts of breast, for example lobular carcinoma and ductal carcinoma [3]. According to the data of Fudan University Shanghai Cancer Center gave out, whether the rate of successfully curing the breast cancer of different type like luminal A, luminal B or HER2 over-expression all higher than 80% (from 84.9% to 93.9%). Provided that the period of breast cancer is under IIIB, the rate will not drop to 80%. Although clinical trials have showed that the vaccines evaluated do not give significant effects, latest researches suggests the possibility of applying vaccines in combination with anti-HER2 monoclonal antibodies or immune checkpoint blockage [4].

Vaccines have been heralded as one of the greatest scientific discoveries of the twentieth century, and they are being utilized for much more than illness prevention: cancer immunotherapy. Cancer vaccination therapy can produce systemic regression of big tumors, extending patients' lives. Although existing immunotherapies (such as immune checkpoint inhibitors and chimeric antigen receptor T cells) have shown promising results in cancer treatment, cancer vaccines have distinct advantages, such as the ability to target intracellular antigens other than tumor-specific surface

antigens and may even elicit new tumor-specific T cell responses. Tumor vaccines, with their unique mechanism of action, are predicted to tackle the clinical treatment dilemma of advanced metastatic breast cancer. This review systematically introduces current therapies for BC and discusses potential vaccines for the treatment of BC.

2. Pathogenesis of breast cancer

2.1. The sketch of pathogenesis of breast cancer

When the proto-oncogenes of breast cancer cells are activated, the connecting tissue between cells is easy to change in structure. In addition, there are abundant capillaries that distribute around breast, which enables shed cancer cells to transfer along blood and lymph. Generally, transferring of cancer cells always accompany severe clinical symptoms with high lethality. Therefore, the prevention of the transfer of cancer cells and the measures that are needed to take when it happened are essential.

2.2. Influencing factors of the incidence of breast cancer

There are a large amount of references about the causative factors of breast cancer, and the interactions between these factors are complex, including physiological, psychological and hereditary factors, and also the individual history, lifestyle and environment. Current researches have illustrated that the incidence of breast cancer of female is closely related to the age of patients. Females age under 24 have a relatively low morbidity, and it will increase as the increase in age. Females age between 50 to 54 are the crowed that have the highest morbidity, while the morbidity will decrease in more older people. By controlling the age, experiments show that people who has fast-paced lifestyle and jobs are highly mentally stressed are more likely to get breast cancer. Besides that, females will higher literacy also have a increased morbidity of breast cancer. This result similar with the result of finding the connection between breast cancer and the emotion of female such as depression and worry. The negative feelings caused by shocks will change the internal environment of patients through stress responses. Furthermore, the immunity will decrease, resulting in the lowering of cell monitoring function and engulfing ability of immune cells, which obviously increase the morbidity of breast cancer. Moreover, consuming pork and mutton is risk factor of onset of breast cancer, while breastfeeding, eat multigrain, consumption of milk and milk products, Soybeans and their products, fresh vegetables and fruits are all protective factors [5].

3. Traditional treatment of breast cancer

Breast cancer is always complex and involving the fusing of surgery, radiation and other treatments that has been researched since it was firstly found. Nonetheless, it is normal that the resistance to systemic therapy appears, therefore, processing individually curing plan is necessary according to the conditions of patient and the tumor. Although the diagnosing and treating of breast cancer have advanced, the management of it is still developing, which focus on the specialized care and the usage of nature compounds. Modified radical mastectomy is the standardized treatment for breast cancer in traditional method, however, breast-conserving surgery is the treatment that patients prefer to choose. Utilizing this therapy prevents the excrescent removing of healthy tissue, which only eliminates the diseased tumor, allowing the side effects of mastectomy more aesthetically bearable [3]. The requirement of taking radiation therapy and adjuvant systemic is decided by the condition of axillary lymph nodes (ALN). Even though ALN dissection was necessary during surgery before the 1990s, it causes a number of negative effects such as swelling, numbness and huge pain that lower the ability of movement of arms [3]. Generally, radiation therapy with the whole breast is accompanied by breast-conserving surgery. To test that, an experiment was set to compare the recurrence rate of breast-conserving surgery with and without the assisting of radiation whether using the adjuvant systemic therapy. As the result, the recurrence rate decreases from 7% to 26% with the use of radiation. In addition, the mortality rate of breast cancer over 15 years seems to decrease (35.9% to 30.5%)

[6].However, the evidences and data are not enough to conclude in a short period. Commonly, chemotherapy is used to treat the node-positive cancer or the cancer with a tumor larger than 1 cm [3].

4. Therapeutic vaccines for breast cancer

Therapeutic Vaccines for Breast Cancer Therapeutic vaccines for breast cancer aim to harness the body's immune system to target and destroy cancer cells. Various types of vaccines have been investigated, including peptide-based vaccines, protein-based vaccines, DNA-based vaccines, and dendritic cell-based vaccines.

4.1. Peptide vaccines

For peptide vaccines, the most presentable one is AE37 breast cancer vaccine, which derived from the intracellular part of HER2 and the core of MHC II. During phase II, research conclude that AE37 vaccine will be eventually used to prevent the relapsing of breast cancer. Over 17 months, the patients who accept AE37 vaccine have an overall decrease in the recurrent rate about 40%. Meanwhile, AE37 vaccine is also targeted on HER2, and is able to reach 84% DFS, when treats HER2 under-expression patients, especially for triple negative breast cancer.

4.2. Protein vaccines

Protein vaccines involve the administration of whole proteins or protein fragments derived from tumor cells to induce an immune response. Comparing with peptide vaccine, using intact protein to make vaccine can avoid the limitation of specific HLA, since it contains HLA I and II expression simultaneously. There is research that has already proved that protein vaccine is able to trigger specific immunity. In a phase I research involving 29 cases of HEER2 overexpressing breast cancer or ovarian cancer, patients were accepted HER2 intracellular domain (ICD) protein vaccine and GM-CSF. It was shown that these protein vaccine has fascinated tolerance. Meanwhile, 89% and 82% patients are able to form specific T-cells and antibody immunity. In another phase I research, 61 cases of II-III phase HER2 positive breast cancer patients who have not consumed trastuzumab accept dHER2 treatment after surgical excision and adjuvant therapy. The result shows that the incidences of dHER2 dosage and dHER2 relative specific humoral immunity are proportional, and 3/4 cases keep the dHER2 specific humoral immunity in the next 5 years after the acceptation of highest dosage of dHER2. Alpha-lactalbumin, the main components of breast milk, is presented by breast cancer cells in a high level, particularly in triple negative breast cancer. Generally, this protein cannot be detected in the females who are no in lactation, however, it can also be detected in triple negative breast cancer patients. Therefore, Alpha-lactalbumin is considered to be the immune target, which enable immune system to attack Alpha-lactalbumin specific expressed cancer cells.

In Duke University, a new vaccine aimed at HER2 named VRP-HER2 vaccine was currently constructed. In phase I, the vaccine was shown that it has excellent tolerance, and no toxin with dosage limitation. The vaccine is currently being administered Phase II clinical study to evaluate vaccination with VRP-HER2 vaccine. The immunotherapy drug pembrolizumab (PD-1 antibody) is also administered at the same time, immunological index in patients with advanced HER2-positive breast cancer and the anti-tumor activity of this treatment strategy.

4.3. DNA vaccines

DNA vaccine is another type of vaccine that refers to the direct injection of a recombinant eukaryotic expression vector of an encoded protein antigen into the body, allowing exogenous genes to be presented in vivo. The antigen produced is able to activate the immune system. Therefore, specific cellular immunity and humoral immunity will be triggered to response. According to a small-scale phase I experiment, there are no side effects or toxicity about vaccinating the DNA vaccine. Although there was no immune response appeared rapidly, MHC II restricted T-cells have an

increased responses in the long-term observation. Additionally, dendritic cells can also be utilized to produce vaccine.

4.4. DC vaccines

Dendritic cells (DCs) are APCs that are capable of presenting exogenous and endogenous antigens to CD4+ T cells and CD8+ T cells, respectively. Currently, it is possible to obtain IDCs carrying TAAs by isolating immature dendritic cells (imDCs) from the peripheral blood of tumour patients and transfecting the DCs with TAAs or vectors encoding TAAs, followed by stimulation of their activation and maturation with specific cytokines, and then The mature dendritic cells are then injected into the patient, and TAAs are presented to CD4+/CD8+ T cells, initiating a robust specific immune response. In a small clinical study, seven patients with stage II-IV HER2 overexpressing breast cancer were vaccinated with HER2 intracellular structural domain (ICD)-stimulated autologous DC vaccine after surgery and completion of 4 weeks of adjuvant therapy. After a mean follow-up of 5 years, anti-ICD antibodies were detectable in 6 patients and all 7 patients survived [7].

5. Conclusions

Despite the potential promise of therapeutic vaccines for breast cancer treatment, several challenges remain to be addressed. These include identifying optimal vaccine antigens, optimizing vaccine delivery and formulation, overcoming immune tolerance and immunosuppression within the tumor microenvironment, and determining the most effective combination strategies with other immunotherapies or standard treatments. Additionally, the development of biomarkers to predict vaccine response and patient selection is crucial for the successful implementation of vaccine-based therapies in clinical practice. Ongoing research efforts are focused on addressing these challenges and advancing the field of therapeutic vaccines for breast cancer treatment. Future directions include the development of novel vaccine platforms, the exploration of combination strategies with other immunotherapies or targeted therapies, and the integration of vaccines into standard treatment protocols.

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