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Passive Vaccination: An emerging tool in immunotherapy of breast cancer

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Invited Editorial

Passive Vaccination: An emerging tool in immunotherapy of breast cancer

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Breast cancer is the most commonly diagnosed and the leading cause of cancer-related deaths among women worldwide [1]"ISSN":"00079235","PMID":"30207593","abstract":"This article provides a status report on the global burden of cancer worldwide using the GLOBOCAN 2018 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer, with a focus on geographic variability across 20 world regions. There will be an estimated 18.1 million new cancer cases (17.0 million excluding nonmelanoma skin cancer. At present, several treatment modalities are in clinical practice, including surgery, hormonal therapy, chemotherapy, radiotherapy, and immunotherapy or targeted therapy etc. These therapies could be in the form of a single therapy or as neo-adjuvant and adjuvant therapies along with surgery and radiotherapies, based on clinical practice guidelines and tumour types. Breast tumours could be luminal-A type (ER^+/PR^+), luminal-B type (ER^+, $/PR^+/HER\text{-}2^+$), HER-2^+ type or basal-like triple-negative type ($ER^-/PR^-/HER\text{-}2^-$) [2]. The majority of breast cancers are luminal-A type, and are generally treated with hormonal therapies such as selective estrogen receptor modulators/blockers, aromatase inhibitors, ovarian suppressants along with surgery and radiotherapy. On the other hand, Luminal-B type of breast cancers are treated by several treatment modalities including hormonal therapy, chemotherapy, and HER-2 targeted therapy apart from surgery and radiotherapy. HER-2 positive breast cancers are metastatic in nature and are difficult to treat. Among several chemotherapeutic agents that are employed to treat these cancers, only monoclonal antibodies (viz: trastuzumab and pertuzumab) and tyrosine kinase inhibitors (Lapatinib) are able to selectively target the HER-2 receptors and kill these cells. Basal-like triple-negative breast cancers are highly metastatic and aggressive in nature and are difficult to contain, as none of the therapies are able to selectively kill these types of cancer cells. However, the only option to treat these types of cancers is to use chemotherapy apart from surgery and radiotherapy (very toxic), and hence, the patients' noncompliance is seen [2].

Immunotherapy is often considered as the better approach in the treatment of breast cancer because of its target specificity and fewer toxicities. It works by stimulating the patients' own immune system against cancer cells. The effectiveness of immunotherapy depends on the ability of individual patient's immune systems, and it may not work equally well as everyone has a different level of immune system. This is evident from the fact that the cancer tumour cells may have innate resistance or have acquired resistance against the cytotoxic T-cells (CTL) due to the expression of PDL1 at different levels on the tumour cells. Immunotherapy can be in the form of artificial antigens/antigen-presenting cells, modified tumour/blood cells, or antibodies/DNAs to induce immunological reactions against tumourcells. Immunotherapy can also be used to enhance the sensitivity of the chemotherapeutic agents in some cancer types. Trastuzumab and pertuzumab, the only HER-2 specific monoclonal antibodies, are approved for the treatment of HER-2 positive breast cancers. Several

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other immunotherapeutic approaches have been tested in clinical trials for the treatment of breast cancers.

Vaccines are emerging strategies in cancer immunotherapy. Breast cancer vaccines are capable of inducing immunological responses against a specific tumour or tumour-associated antigens. The implication of the first cancer vaccine, Sipuleucel-T, was based on the concept of antigen-presenting cells (APCs) [3]. These cells include a heterogenous group of white blood cells (i.e., B lymphocytes, macrophages, and dendritic cells, etc.), which mediate cellular immune responses upon recognition by certain lymphocytes (T-lymphocytes such as CD4 and CD8 cells) after processing and presenting antigens on their surfaces. Among them, dendritic cells are more potent in presenting an antigen and initiating anticancer activities from naïve T-cells as well as memory T-cells [4]. The APCs first engulf the invaders or foreign bodies to take them into the cytoplasm, where they are broken down into small fragments to process them into antigens (peptides). These peptide-antigens are then loaded onto the Class I or Class II MHC molecules to present the antigens to T-cells. While the CD4-Th cells recognize the antigen loaded onto the MAC Class II molecules on the surface of the APC-cells through the T-Cell Receptors, the CD8 cells engage the antigen loaded onto the Class I MHC molecules on the surface of the APCs or cancer-tumour cells. Based on the nature of the antigen involved, the CD4 cells, so activated by the APCs, may induce the cell mediated immunity (activation of macrophages, CTLs, NK cells) through the release of cytokines (such as INFγ, TNFβ, IL2, IL12), or activate the humoral immunity, through the cytokines such as IL4, IL5, IL6, IL10, to cause the release of antibodies. On the other hand, the CD8 cells (CTLs), upon activation, causes the release of performins and granizymes, which induce the apoptosis on the target cells (APC or tumour cells). Hence, all of the tumour cell vaccines have been modified genetically to express chemokines, cytokines, or other costimulatory molecules to stimulate the immune responses against the tumour cells [5].

Passive vaccination refers to the process of transferring the activated T-lymphocytes, natural killer cells or ready-made antibodies as active humoral immunity. The adoptive T-cell transfer technique is a novel approach in cellular immunotherapy, in which peritumoral T-lymphocytes are extracted from the body and then cultivated and activated for transfusion. These activated cells can produce a long-lasting response in more than 25% of cancers [6]the infusion of large numbers of activated autologous lymphocytes, can mediate objective tumor regression in a majority of patients with metastatic melanoma (52 of 93; 56%. In clinical studies, researchers have isolated the tumour antigen-specific CD8+ T-lymphocytes from patients' bone marrow and re-transfused after activation. About 50% of the metastatic breast cancer patients showed a significant immunological response and overall survival as well [7,8]there has been an increased interest in optimizing this technology in order to make it a clinically feasible treatment. One of the main treatment modalities within cancer immunotherapy has been adoptive T cell therapy (ACT.

Although natural killer cells possess less potential than T-lymphocytes, they could still be used for passive vaccination. As natural killer cells do not express many surface markers, they can be useful in helping dendritic cell-based vaccines. However, in many studies, stem cell-derived natural killer cells have shown better cytotoxic potential against cancer cells [9–11]. Moreover, these cells have also shown synergistic potential with chemotherapeutic agents in metastatic breast cancer patients [12].

Another interesting perspective, of the adoptive T-cell transfer technique, in which the T-cells represent chimeric antigen receptors on their surfaces, is also studied. In this regard, the T-cells are extracted from the patients and transfected with genes that encode particular types of proteins to express on their cell surface as receptors that can be recognized by immune cells and then re-administered into the patients to initiate immunological responses against cancer cells. For the first time, the FDA has approved chimeric antigen receptor T-cells as the first cell-based immunotherapy for leukemia patients

due to their clinical effectiveness in a randomized clinical trial [13].

More efforts have been made to develop ready-made antibodies such as trastuzumab and pertuzumab more effectively for the treatment of HER-2-positive breast cancers. These monoclonal antibodies specifically bind to HER-2 receptors and attract immune cells to kill these particular types of cells. In the clinical setting, trastuzumab, as a single adjuvant therapy or in combination with chemotherapy, showed greater effectiveness and reduced recurrence rate in 50% of the HER-2 positive breast cancer patients [14]. Pertuzumab has also been approved as a single therapy as well as in combination with docetaxel and trastuzumab for the treatment of HER-2 positive breast cancer [15].

The whole concept of cancer vaccination depends on the patient's immune system and cancer types. Among all the breast cancer types, triple-negative breast cancer is the most immunogenic and expresses more MHC Class I molecules on their cell surfaces, which helps in being recognized by the T-lymphocytes (CTL); whereas, luminal-A type of breast cancer cells express very low levels of MHC-I and are dependent on estrogen for their growth. These cells are the least immunogenic, which can be poorly recognized by immune cells and hence, are less responsive to the immunotherapy. Monoclonal antibodies that are widely involved in the therapy of breast cancer, such as trastuzumab and pertuzumab, target the membrane receptors HER-2; whereas, atelizumab, which is used against triple-negative breast cancers, acts as a checkpoint inhibitor. But its clinical utility is needed to be proven. Moreover, chemotherapy in combination with immunotherapy, has been shown to be more effective and hence, the direct or indirect mechanism for improving the immune reactivity of chemotherapy is now becoming interesting and needs to be evaluated. The vaccine therapy could be a great option for the immunotherapy, for the prevention as well as the treatment of breast cancer in the future.

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