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Emerging Innovations in Cancer Immunotherapy
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Cancer Is a Word, Not a Sentence!

In last two decades, a great stride of improvement is noticeable with respect to women empowerment and gender equality in India. Unfortunately, many productive women are becoming a victim to the dreaded disease; **C**ancer. Cancer burden has doubled in the last 26 years in India. With rising life expectancy, cancer has made its vital place in our society and this burden is not only limited to disease but also leads to an economic loss for the nation. Among Indian women, breast cancer is currently the most common and accounts for ~ $1/4^{th}$ of all cancers. And with over 60% of the cases being diagnosed in the advanced stage, clinical reports by health ministry suggests that breast cancer ranks number 1 among Indian females globally.

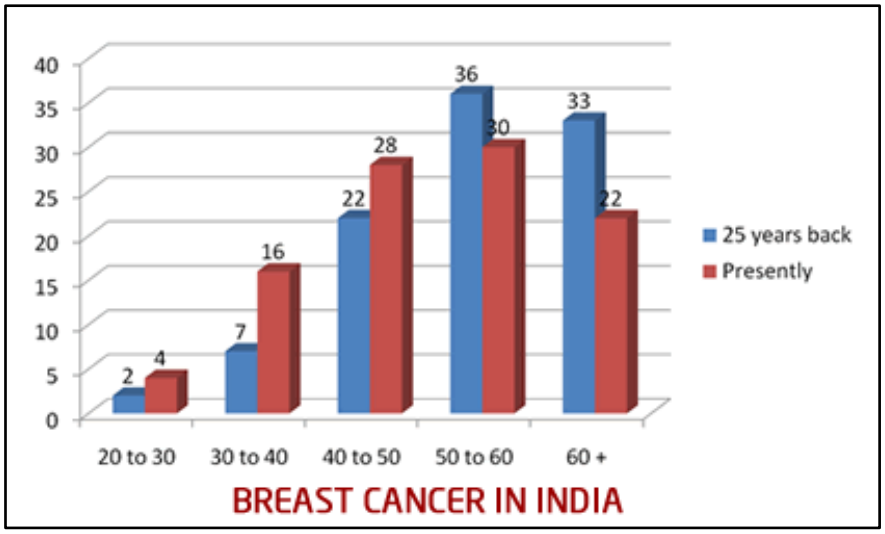

Figure 1: Increasing Incidence of Breast Cancer among Younger Age Groups. The horizontal line lower down represents the age groups and the vertical line represents percentage of cases. An increasing number of patients are in the 25 to 40 years of age.
(*Image adapted from* ***breastcancerindia.net***)

Major Causes

With changing lifestyle coupled with hormonal imbalance, late pregnancy, lack of breastfeeding, early menarche (start of menses), late menopause (stopping of menses), alcohol, obesity, lack of exercise, medical use of hormones and stress, all increase the risk of breast cancer. Another important factor is strong family history. The is due to the presence of mutation of genes such as ***BRCA1*** or ***BRCA2*** which pass on to next generations. The rate of acquiring *BRCA* gene mutation ranges between 2-24% among Indian women. Symptoms of breast cancer include massive lump or a mass in the breast, along with prolonged swelling, pain and skin irritation. Physical examinations along with mammogram, ultrasound and biopsy analysis are most commonly employed detection methods. The importance of self-examination along with regular check-ups after the age of 40 is globally advised to avoid late detection.

Conventional

The conventional treatment comprises of surgical resection of the tumor along with chemotherapy, radiotherapy and/or hormonal therapy. Even after the completion of

treatment, patients diagnosed with advanced stage cancer are still at a higher risk of cancer relapse.

Immunotherapy

Our immune system actively works to protect us against diseases, including cancer. It usually identifies faulty cells and destroys them but sometimes the immune system *misses* or *fails* to recognize these altered cells leading to disease progression. Scientists are working on ways to trigger the immune system so it can recognise cancer cells and mount an immune response. There are a few different types of targeted drug treatments for advanced breast cancer. Some target a particular part of the cancer cell, others uses the immune system to kill cancer cells.

Clinical findings suggest that 3 out 10 patients diagnosed with advanced stage breast cancer have high amounts of protein Human Epidermal Growth Factor 2 (HER2). Moreover, blocking the expression of HER2 protein can significantly reduce cancer cell multiplication and progression. Monoclonal antibodies such as ***Atezolizumab***, ***Trastuzumab***, ***Pertuzumab***, **and** ***Denosumab*** are often recommended to patients to stop cancer cells from growing and dividing.

Programmed cell death ligand protein 1 (PD-L1), the ligand for PD1, is highly expressed in several cancers that exhibits an immunosuppressive effect. Inhibiting the interaction between PD-1 and PD-L1 can enhance anti-tumor activity against the cancer cells. Checkpoint inhibitors such as PD-1 could be used along with other MAbs to activate immune cells to attack tumor. These therapies can be prescribed to patients either alone or in combination with chemotherapy or hormonal therapy.

Dendritic Cell (DC) based Immunotherapy

Since MAbs target specific epitopes, these epitopes may vary in expression from patient to patient. Furthermore, Mabs fail to reduce anti-inflammatory cytokine levels or generate an effective memory response in the cancer patient as they do not recruit any Antigen Presenting Cells (APCs). In order to overcome these problems and to improve the immune function, itwould be better to utilize Dendritic cells (DCs) taken from the patient and manipulated ***ex vivo***. The process involves isolation of patient's monocytes by Leukapheresis along with differentiation into immature DC's using a maturation cocktail of growth factors. These cells are matured by loading with tumor associated and tumor specific antigens isolated from patient by biopsy. The use of ***ex vivo***-generated DCs is profitable, because it enables overcoming the difficulties resulting from compromised immunological function by allowing the development of an adequate immune response against the tumor. DCs in breast cancer are capable to provide a memory response to tumor

antigens and to inhibit the tumor growth.DC based immunotherapy has been shown to be safe and effective in treating patients with metastatic disease. It has demonstrated to provide survival benefit in several cancer indications such as GBM, RCC, Prostate, Lung, Head and Neck and Colorectal cancer. After preclinical success, several clinical trials are being conducted to investigate the safety and efficiency of DC based immunotherapy in metastatic breast cancer patients.

The first clinical evidence for the activity of DC vaccine in breast cancer patients was reported by ***Brossart et al***. The pilot study revealed the safety and efficacy of DC vaccinations among patients with advanced breast disease and tumors expressing **HLA-A2** and **HER2** or **MUC1** who were administered peptide-pulsed DCs subcutaneously. Immune response was detected by the presence of peptide-specific CTLs suggesting effective anti-tumor immune response for DC therapy. A recent phase II clinical trial demonstrated that DC therapy administered along with low doses of IL-2 was safe and helped in boosting an effective memory response in patients against cancer cells.

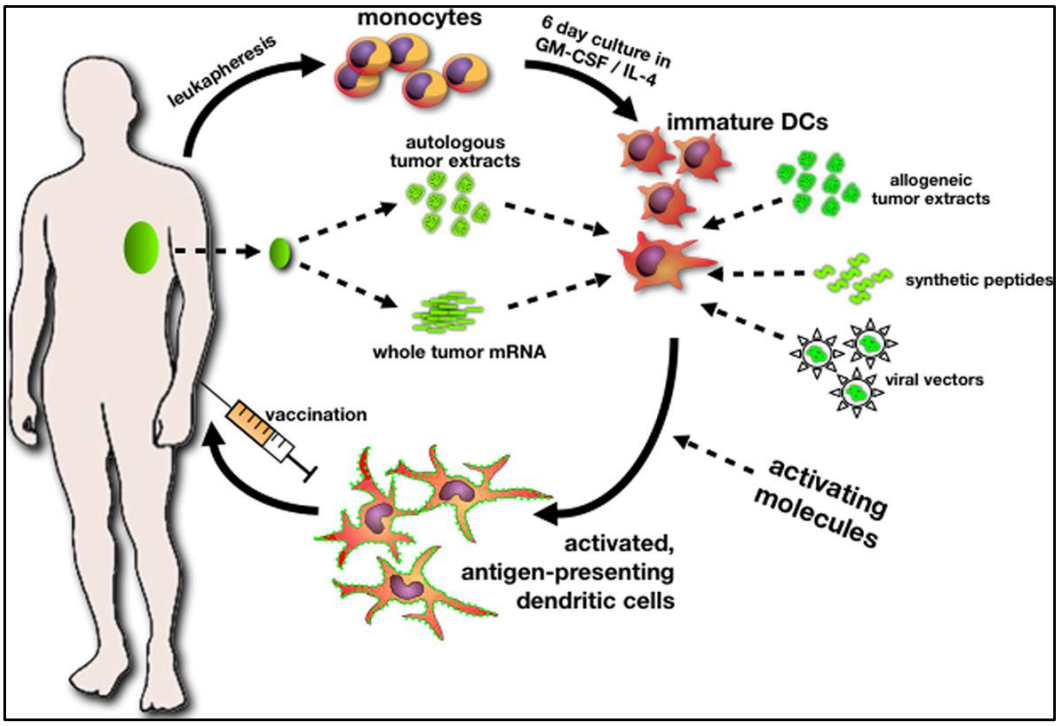

Figure 2: Generation of DC based Immunotherapy in cancer treatment.
To activate CTL in an immunosuppressive environment, DC based immunotherapy is being designed and employed to induce an amplified immune response against the cancer cells (Adapted from – '***Investigational approaches for mesothelioma'***).

Czerniecki et al conducted a clinical trial among 11 patients using DCs pulsed with HER2/*neu* HLA class I and II peptides, administered to patients with *HER2-positive ductal carcinoma in situ* (DCIS) before surgical resection. Of 11 evaluable patients at those dose levels, 6 patients (54%) had clinical benefit; this included one complete response lasting 89 weeks and one partial response lasting 24 weeks and four patients had stable disease (Figure 3). The results of the research were presented at the International Cancer Immunotherapy Conference (2019), held in New York.

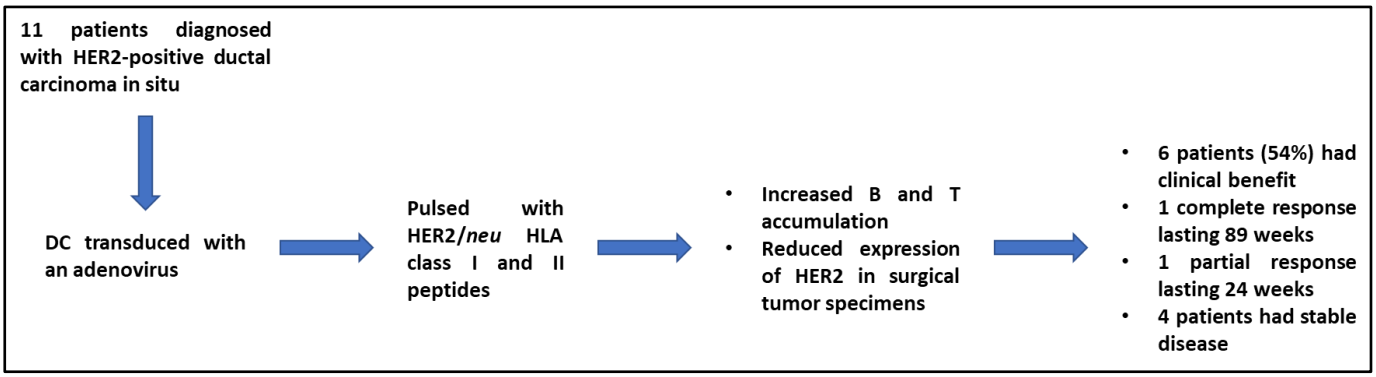

Figure 3: Phase I trial investigating the use of DC based immunotherapy among patients diagnosed with *HER2-positive ductal carcinoma in situ* (DCIS).

Further studies are also underway to assess the potential of DC immunization to synergistically interact with other forms of medical treatment, such as chemotherapeutic compounds (e.g., vinorelbine or cyclophosphamide) or targeted therapy. Currently 3 trials have started assessing the combination of two or more therapeutic strategies with different mechanisms of action that may stimulate the immune system in different ways in order to evoke a strong and specific response to stop tumor cells from growing.

What the future holds

DC-based immunotherapy is evolving dynamically and offers a promising therapeutic approach for breast cancer patients. DC vaccines have shown to be able to up-regulate antigen-specific immunity *in vivo*. Molecular typing of cancer as well as combinatorial therapies seems to develop a growing interest in testing activity along with tolerability for the combination treatment of Immunotherapy with standard breast cancer treatments such as chemotherapy and targeted and radiation therapy. Combination approach could be also useful to improve the specific response of therapy as it will induce both cancer-specific immune activation and mediate inhibition of immune tolerance.