Review Article

Advances on immunotherapy in breast cancer

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Abstract: Since its inception in the 1940's, chemotherapy has remained the standard treatment for many cancers. The morbidity and mortality associated with these drugs have triggered scientists to discover newer methods of treatment such as immunotherapy. Although immunotherapy has proven to be successful in many preclinical and clinical models in cancers such as melanoma, data in poorly immunogenic cancers such as breast cancer continues to be controversial. Several large clinical trials have tested the use of various forms of immunotherapy in breast cancer such as checkpoint inhibitors, adoptive T cell therapy, vaccines and adjunctive immunotherapy, all of which have shown promising results. This review article highlights the advances of immunotherapy in breast cancer and discusses the future research needed to be conducted to unveil the full potential of these drugs.

Keywords: Immunotherapy; breast cancer; checkpoint inhibitors; adoptive T cell therapy; cancer vaccines; cytokines; adjunctive immunotherapy; CAR-T cells

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Introduction

Since its inception in the 1940s (1), chemotherapy has evolved to be a cornerstone in the treatment of many cancers. One of the major disadvantages to chemotherapy has been the considerable toxicity. This has led scientists to discover newer, targeted methods of cancer treatment, such as immunotherapy.

Immunotherapy uses biologic agents to control the signals that dictate cell growth and bolster the natural immune response to malignancy (2). Although breast tumors have historically been deemed immunologically silent, some subtypes have shown interactions with the immune system, the modulation of which may result in effective antitumor activity (3,4). The role of immunotherapy in breast cancer, the mechanism of action of immunotherapeutic agents, and their clinical relevance is discussed in this review article.

Effect of tumor cells on the immune system

In order to prevent autoimmunity, regulatory cells, such as myeloid derived suppressor cells [MDSC] and CD4+CD25hiFoxP3+ T cells [Tregs] exist to suppress self-recognition of T-cells. Tumor cells are able to evade the immune system by differentiating these regulatory cells and increasing their levels (5). In addition to enhancing immunosuppression through Treg cells and MDSCs, tumor cells also escape the immune system by decreasing the levels of antigen presenting cells and increasing the expression of proteins such as anti-apoptotic proteins (survivin, BCL-XL), metastatic proteins (VEGF, MMPs) and proliferation factors (EGFR, c-Myc) (6).

Checkpoint inhibitors, adoptive T cell therapy, and therapeutic vaccines are immunotherapeutic agents that are able to counteract this tumor-induced immunosuppression.

Immunotherapy and breast cancer

Recent studies have identified the presence of tumor infiltrating lymphocytes (TILs) in breast tumor tissue to be a prognostic factor for the pathological complete response (pCR) to neoadjuvant chemotherapy (NAC) (7). With 1,058 patient biopsies, Dushyanthen *et al.*, demonstrated higher post-NAC pCR rates in TIL+ tumors than TIL- tumors (40–42% *vs.* 3–7%) (7). In this study, more than 60% TILs were present in either the stromal or intratumoral component of the tissue. This response has also been documented in triple negative and HER-2 positive breast cancers.

In addition to the chemotherapeutic agents like taxanes and anthracyclines, some studies have also demonstrated the correlation between TIL and trastuzumab. Loi *et al.*, randomized 232 patients with HER-2 positive disease to either trastuzumab in combination with chemotherapy or chemotherapy alone (8). Results showed a decrease in distant recurrence with each 10% increase in TILs in the combination arm. Salgado *et al.* also reported similar data with higher pCR rates with TILs higher than 5% and a 3% decrease in an event for every 1% increase in TILs (9). Here the patients were randomized to one of three groups: trastuzumab, lapatinib, or the combination for 6 weeks followed by the addition of weekly paclitaxel for 12 weeks, and 3 cycles of fluorouracil, epirubicin, and cyclophosphamide after surgery. Although the correlation between TILs and pCR was seen in all breast cancer subtypes, the correlation between TILs and disease free endpoints was only seen in triple negative and HER 2 positive subtypes (7). These results have not only identified new prognostic markers for certain breast cancer subtypes but have also highlighted the immunological activity in a cancer that was originally deemed immunologically silent.

Ali *et al.* conducted one of the largest breast cancer immunotherapy studies where 12,439 breast cancer cells were tested for CD8 and FOX3 immune markers. Breast cancer tissue with CD8+ T cells showed a 28% reduction in hazard of breast cancer-specific mortality in ER-negative tumors (n=2,402), 27% reduction of breast cancer-specific mortality in ER-positive/HER 2-positive tumors (n=483), but no difference in survival in the ER-positive tumors (n=5,956) (10). The study concluded that some subgroups, such as ER-negative tumors and ER-positive/HER 2-positive tumors, could benefit from immune modulation (10).

Checkpoint inhibitors

Immune checkpoints, in the normal physiological state, cause T cell inactivation thus allowing self-tolerance (1). Tumor cells manipulate this mechanism to escape recognition by the immune system (1). Checkpoint inhibitors targeting CTLA-4, PD-1 and PD-L1 prevent this T cell inactivation.

CTLA-4 antibodies have shown mixed responses. Negative results were reported with the use of CTLA-4 antibodies in breast cancer cell lines, TSA, 4T1 and SM1 (11) which are poorly immunogenic. A partial response was however achieved with EMT6 cell line (11). In a small study, tremelimumab, a monoclonal antibody against CTLA-4, in combination with exemestane, an aromatase inhibitor, resulted in stable disease for at least 12 weeks in 42% of patients (12). Further studies showed that responses may be limited to moderately immunogenic cell lines. CTLA-4 blockers have also been studied in combination with radiation and have shown enhanced tumor response at the primary site and growth inhibition at sites outside the radiation field. This study is discussed further under adjunctive immunotherapy.

A large 2016 study involving 111 triple negative breast cancer patients tested the antitumor activity of the PD-1 inhibitor, Pembrolizumab (13). Among the 27 patients that were evaluable, 18.5% demonstrated antitumor activity based on RECIST v1.1 and the median time to response was 17.9 weeks (13). Adams *et al.* reported promising results with azetolizumab (an anti-PD-L1 inhibitor) in combination with nab-paclitaxel in metastatic triple negative breast cancer (mTNBC). Of the 24 evaluable patients, 7 out of 9 patients with 1 lesion, 6 out of 8 with 2 lesions, and 3 out of 7 with 3 or more lesions showed partial response. A total of 5 patients showed stable disease (14). All patients received ≤3 prior lines of therapy. A clinical trial with azetolizumab plus nab-paclitaxel in the first line setting for mTNBC is ongoing with Progression Free Survival and Overall Survival as primary endpoints.

The combination of CTLA-4 inhibitors and PD-1 inhibitors is currently being tested in various settings such as Nivolumab and Ipilimumab in advanced or metastatic HER2-negative breast cancer (NCT02453620), Durvalumab and Tremelimumab in advanced tumors, including triple negative breast cancer (NCT02527434) and Durvalumab and Tremelimumab in patients with metastatic HER 2-negative breast cancer (NCT02536794). A comprehensive list of all check point inhibitor studies in breast cancer can be found in *Table 1*.

Table 1 Ongoing and future phase 1 and 2 programmed death/programmed death ligand clinical trials in breast cancer with associated ClinicalTrials.gov identifier

Currently enrolling PD clinical trials
Safety and tolerability of recombinant humanized anti-PD-1 monoclonal antibody for patients with advanced breast cancer (NCT02838823)
Phase I/II study of the anti-programmed death ligand-1 antibody MEDI4736 in combination with olaparib and/or cediranib for advanced solid tumors and advanced or recurrent ovarian, triple negative breast, lung, prostate and colorectal cancers (NCT02484404)
Phase I/II study of PDR001 in patients with advanced malignancies (NCT02404441)
Neoadjuvant MEDI4736 concomitant with weekly nab-paclitaxel and dose-dense AC for stage I-III triple negative breast cancer (NCT02489448)
Safety Study of nivolumab with nab-paclitaxel plus or minus gemcitabine in pancreatic cancer, nab-paclitaxel/carboplatin in stage IIIB/IV non-small cell lung cancer or nab-paclitaxel in recurrent metastatic breast cancer (NCT02309177)
A study of CA-170 (oral PD-L1, PD-L2 and VISTA checkpoint antagonist) in patients with advanced tumors and lymphomas (NCT02812875)
A phase II single arm pilot study of the Chk1/2 inhibitor (LY2606368) in BRCA1/2 mutation associated breast or ovarian cancer, triple negative breast cancer, high grade serous ovarian cancer, and metastatic castrate-resistant prostate cancer (NCT02203513)
Pembrolizumab and doxorubicin hydrochloride or anti-estrogen therapy in treating patients with triple-negative or hormone receptor-positive metastatic breast cancer (NCT02648477)
Adjuvant PVX-410 Vaccine and Durvalumab in Stage II/III Triple Negative Breast Cancer (NCT02826434)
A combination clinical study of PLX3397 and pembrolizumab to treat advanced melanoma and other solid tumors (NCT02452424)
A Study of PDR001 in combination with CJM112, EGF816, canakinumab or trametinib (NCT02900664)
RADVAX: a stratified phase I trial of pembrolizumab with hypofractionated radiotherapy in patients with advanced and metastatic cancers (NCT02303990)
Study of niraparib in combination with pembrolizumab (MK-3475) in patients with triple-negative breast cancer or ovarian cancer (NCT02657889)
Safety study of nivolumab with nab-paclitaxel plus or minus gemcitabine in pancreatic cancer, nab-paclitaxel/carboplatin in stage IIIB/IV non-small cell lung cancer or nab-paclitaxel in recurrent metastatic breast cancer (NCT02309177)
Abrogation of chronic monoclonal antibody treatment-induced T-cell exhaustion with DURVALUMAB in advanced HER-2 negative breast cancer (NCT02802098)
Study of Pembrolizumab (MK-3475) Plus Chemotherapy vs. Placebo Plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer (MK-3475-355/KEYNOTE-355) (NCT02819518)
Safety study of enoblituzumab (MGA271) in combination with pembrolizumab in refractory cancer (NCT02475213)
Pembrolizumab combined with INCB039110 and/or pembrolizumab combined with incb050465 in advanced solid tumors (NCT02646748)
Pembrolizumab, letrozole, and palbociclib in treating patients with stage IV estrogen receptor positive breast cancer with stable disease that has not responded to letrozole and palbociclib (NCT02778685)
Safety and efficacy study of pembrolizumab (MK-3475) in combination with chemotherapy as neoadjuvant treatment for participants with triple negative breast cancer (TNBC) (MK-3475-173/KEYNOTE 173) (NCT02622074)
A Phase I/II study of MEDI4736 in combination with olaparib in patients with advanced solid tumors. (MEDIOLA) (NCT02734004)
Future PD clinical trials
A Study of PDR001 in combination with LCL161, everolimus or panobinostat (NCT02890069)
A Study of FAZ053 single agent and in combination with PDR001 in patients with advanced malignancies (NCT02936102)
Addition of PD-L1 antibody MEDI4736 to a taxane-anthracycline chemotherapy in triple negative breast cancer (GeparNuevo) (NCT02685059)
A Study of FAZ053 single agent and in combination with PDR001 in patients with advanced malignancies (NCT02936102)
Randomized phase 2 study of atezolizumab and entinostat in patients with aTN breast cancer with phase 1b lead in (NCT02708680)
Veliparib and atezolizumab either alone or in combination in treating patients with stage III-IV triple negative breast cancer (NCT02849496)

Adoptive T cell therapy

Adoptive T cell therapy, also referred to as passive immunization, involves the isolation and ex vivo expansion of tumor specific T cells (14). T cell priming with cancer vaccines (active immunization) prior to isolating the T cells from the patient's blood has shown great success in expanding the T cell population (15). Adoptive T cell therapy using tumor-infiltrating lymphocytes (TIL), cytotoxic T lymphocytes (CTL), Th cells, Tregs and genetically engineered T cells have shown promising results in melanoma (15). These studies have now been expanded to other cancer types including breast cancer.

The Tumor Vaccine Group at the University of Washington, identified Th1 cells to be superior to CTLs due to their ability to activate antigen-specific effector cells, recruit macrophages and dendritic cells to assist in antigen presentation, directly and indirectly (through cytokines like IL-2) activate CTLs, produce opsonizing antibodies that enhance the uptake of tumor cells into APC, and most importantly initiate epitope spreading (15). In a clinical trial with 16 metastatic breast cancer patients, Domschke *et al.* identified high levels of tumor-reactive memory T cells in the bone marrow that could have therapeutic effect once re-stimulated *ex vivo* (16). Tumor-reactive memory T cells in the peripheral blood were induced in 7 out of 16 patients (44%) after the adoptive cell transfer of bone marrow T cells. These patients were deemed responders. Patients with an immunologic response in the peripheral blood had a significantly longer median survival than non-responders (median survival 58.6 *vs.* 13.6 months; P=0.009). This positive response was only seen in patients without bone metastasis.

As isolation of tumor specific T cells is difficult, genetically engineered or redirected T cells have been of interest in recent times as a form of adoptive T cell therapy. Genes that encode T cell receptors are used to generate tumor specific T cells. This is done using either the alpha or beta chain of the T cell receptor or using chimeric antigen receptors (CAR) (17). CARs are composed of an extracellular domain derived from tumor-specific antibody, linked to an intracellular signaling domain. Plasmid transfection, and mRNA or viral vector transduction are used to introduce these genes into T cells to generate tumor specific T cells. These genetically modified and activated T cells are then reintroduced into the patient's blood to target specific tumor proteins.

CAR T cell technology in solid tumors is still largely in the preclinical phase with Tumor Associated Antigen (TAA) identification posing the greatest challenge. Neoantigens, which are products of tumor mutations, have been of particular interest as their expression is restricted to only tumor cells (18). In a preclinical study, Tchou *et al.* tested the CAR technique in triple negative breast cancer tissue. 67% of triple negative breast cancer samples showed overexpression of mesothelin, a glycoprotein (19). An in vitro killing assay was done to assess the cytotoxicity of genetically modified T cells expressing CAR for mesothelin versus a non-transduced T cell. About 31.7% cytotoxicity was observed by the mesoCAR T cells, as opposed to 8.7% cytotoxicity for non-transduced T cells (19). A 2016 study by Song *et al.* identified the folate receptor alpha (FRα) to be a promising target (20). It was found that FRα specific CAR T cells in the setting of TNBC showed significant tumor growth inhibition in immunodeficient mice bearing MDA-MB-231 tumor xenograft (20).

Most CARs incorporate the T cell receptor CD3ζ signaling chain to cause cytotoxicity (21). A study was conducted where CD28 mediated signaling aimed at T cell proliferation and IL-2 production was incorporated to study the benefit of complimentary CAR T cells (22). These cells were then engineered to co express ErbB2- and MUC1 and tested in breast cancer. Results showed efficient proliferation of T cells and destruction of ErbB2 positive tumor cells and confirmed the benefit of the dual target approach using CAR T cells. A unique approach of combining PD-1 inhibitors with CAR T cells to enhance the therapeutic outcome is also being tested using mouse models.

A list of ongoing CAR T cell clinical trials in breast cancer can be found in *Table 2*.

Vaccines

The success of vaccines for viral diseases has provided the frame work for developing vaccines for cancers. Cancer has been associated with T cell deletion and T cell anergy causing defective memory (23). The aim of vaccines has been to prepare naïve T cells and transform the existing memory T cells into effective combatants of the tumor cells. In order to prepare naïve T cells, tumor antigens have to be presented using MHC class 1 and 2 (23). With dendritic cells being the most efficient antigen presenting cells, many clinical trials have employed plasmacytoid dendritic cell vaccines and conventional dendritic cell vaccines (23). Plasmacytoid dendritic cells (pDCs), in addition to

Table 2 Ongoing chimeric antigen receptor clinical trials in breast cancer with associated ClinicalTrials.gov identifier

Currently enrolling CAR T cell clinical trials in breast cancer
Chimeric antigen receptor-modified T cells for breast cancer (NCT02547961)
EpCAM CAR-T for treatment of nasopharyngeal carcinoma and breast Cancer (NCT02915445)
A clinical research of CAR T cells targeting CEA positive cancer (NCT02349724)
Phase I/II study of anti-mucin1 (MUC1) CAR T cells for patients with MUC1+ advanced refractory solid tumor (NCT02587689)
Genetically modified T-cell therapy in treating patients with advanced ROR1+ malignancies (NCT02706392)
A clinical research of CAR T cells targeting HER2 positive cancer (NCT02713984)
Treatment of relapsed and/or chemotherapy refractory advanced malignancies by CART-meso (NCT02580747)
Treatment of relapsed and/or chemotherapy refractory advanced malignancies by CART133 (NCT02541370)

being antigen presenting cells, can also alter the tumor microenvironment and have shown IFN-1 dependent tumor regression through TLR7 ligand and IFN-1 independent tumor regression through TLR9 ligation (23).

Although the mouse models have shown positive results using activated pDC in the setting of melanoma and sarcoma tumors, dendritic cell involvement in human cells did not show a favorable outcome. T cell and dendritic cell infiltration into human breast cancer cells was assessed in 152 patients with invasive non-metastatic breast cancer using DC migration markers (MIP-3a/CCL20, MIP-3b/CCL19, and 6Ckine/CCL21), CD1a (T cell), CD3 (T cell), CD68 (Macrophages), CD123 (plasmacytoid Dendritic cells), CD207/Langerin (immature dendritic cells), and CD208/DC-LAMP (mature dendritic) expression (24). CD 123 infiltration in the tumor was associated with shorter overall survival (93% versus 58% at 60 months) and relapse free survival (90% *vs.* 37% at 60 months) (24). CD208/DC-LAMP positive DC (56%) and CD3 positive T cells (82%) strongly correlated with lymph node involvement (24). The mechanism behind this negative effect on human breast cancer cells was studied using 60 human breast cancer biopsies where increased tumor associated pDC (TApDC) were seen in aggressive cancer cells. TApDC expressed very low levels of interferon alpha which caused FOX3p+ Treg expansion leading to the immune tolerance (25). With interferon alpha being a strong immunomodulator and FOX3p+ Treg having immunosuppressive qualities, the negative response in human breast cancer cells was justified.

Knowing the poor immunogenic quality of breast cancer cells, Abe *et al.* identified a subpopulation of the 4T1 mouse breast cancer cell line, 4T1-Sapporo (4T1-S), which showed immunogenic properties when used to vaccinate mice (26). The mice were vaccinated with 4T1-S prior to receiving injections with the same cell line and showed significant enlargement of draining lymph nodes and increased frequencies of activated CD8 T cells (26). This mouse model helped in identifying the benefit of cancer vaccines after enhancement of the immunogenic properties of breast cancer cells.

In a clinical trial, 22 patients with Stage 4 HER2/neu positive breast cancer received HER2/neu T-helper peptide-based vaccine in addition to Trastuzumab which resulted in epitope spreading within HER2/neu and other proteins. The T cell response was also inversely proportional to the level of transforming growth factor beta (a promoter of tumor growth and metastasis) (27). A phase 1–2 clinical trial was conducted to assess the clinical benefit of E75 vaccine (a human leukocyte antigen (HLA) A2/A3-restricted HER2/neu (HER2) peptide, and granulocyte-macrophage colony-stimulating factor) on patients with HER2/neu positive breast cancer that either were lymph node positive or were high risk. Only HLA-A2/A3(+) patients were vaccinated. Out of 195, 182 patients were evaluable. Disease free survival was 94.3% in the vaccinated group and 86.8% in the control group (P=0.08) (28). A booster dose was also initiated and none of the patients who received the booster dose had a recurrence (28). The scope for booster treatments due to its low toxicity profile has shown a promising future for cancer vaccines.

Certain cytokines have proven to have synergy with cancer vaccines. Low levels of TNF- alpha production has been seen in breast cancer patients in comparison to healthy individuals (29). It has been found that DC infiltration is dependent on TNF alpha production and low levels of TNF alpha impair their ability to recruit naïve T cells (29). Other studies have shown an increase in the apoptosis of tumor cells with the co administration of TNF alpha and DC (29). It has also been reported that DCs which have been activated by pro-inflammatory cytokines produce

Table 3 Ongoing clinical trials in breast cancer with adjunctive therapies using radiation and cytokines and associated ClinicalTrials.gov identifier

Radiation with PD-1/PD-L1 inhibitor
Pilot Study of stereotactic ablation for oligometastatic breast neoplasia in combination with the Anti-PD-1 antibody MK-3475 (NCT02303366)
Study to assess the efficacy of pembrolizumab plus radiotherapy in metastatic triple negative breast cancer patients (NCT02730130)
Nivolumab after induction treatment in triple-negative breast cancer (TNBC) patients (NCT02499367)
Radiation with TGF-beta and GM-CSF
LY2157299 monohydrate (LY2157299) and radiotherapy in metastatic breast cancer (NCT02538471)

TNF-alpha, leading to apoptosis in breast cancer cells (29).

Adjunctive immunotherapy

Although most chemotherapies cause immunosuppression, some drugs help in increasing the tumor immunogenicity and can be coupled with other immunomodulators, such as immunostimulatory cytokines, to achieve the maximum antitumor effect. Doxorubicin, for example, upregulates MHC class 1 and Fas expression and increases sensitivity to Cytotoxic T Lymphocyte killing (30). Other anthracyclines and platinum salts release high-mobility group box 1 (HMGB1) and adenosine triphosphate (ATP) which result in the release of IL-1β and activation of Toll ligand receptor 4 (TLR4) on the infiltrating dendritic cell (31). The activated TLR4 then stimulates innate immunity while IL-1β takes part in cell proliferation, differentiation and apoptosis (31). Taxanes have shown to increase the lymphocyte infiltration when given neoadjuvantly and also increase the Th1 associated cytokines when given in the metastatic setting (30).

IL-18 is one immunostimulatory cytokine that has demonstrated the ability to enhance the production of IFN-γ by the T cells and natural killer cells, act synergistically with IL-12 to induce IFN-γ production, augment the cytolytic activity of natural killer cells and CTLs, promote the differentiation of activated CD4 T cells into helper effector cells, and stimulate Th1 immune responses (32,33). IL-18 is able to augment the activity of phase specific chemotherapeutic drugs that are unable to target resistant tumor cells in a non-vulnerable phase of the cell cycle (34).

Divino *et al.* used an intrahepatic tumor model of metastatic breast cancer to test the effects of intravenous administration of recombinant adenoviral vector expressing the murine IL-12. Prolongation of long term survival of IL-12 treated animals, with complete tumor rejection in 40% of the animals was reported (35). This study clearly showed the benefit of immunostimulatory cytokines in metastatic breast cancer.

In 2014, a study was conducted on 90 post mastectomy triple negative breast cancer patients where cytokine induced killer (CIK) cell infusion was used in conjunction with chemotherapy (36). CIK adjuvant therapy showed an increase in disease free survival in patients with pathologic grade 3 disease, and increase in overall survival in N1, N2, N3, IIB, III TNM stages as well as pathologic grade 3 disease (36).

Radiation has also shown some immunomodulatory effects causing upregulation of the expression of MHC and the radiation induced tumor epitopes. In the first preclinical study to test Radiation with CTLA-4 inhibitor (Ipilimumab) in a metastatic 4T1 breast cancer model, the inhibitor alone did not show regression of tumor due to poor immunogenicity of breast cancer cells but the combination showed tumor shrinkage and inhibition of lung metastasis (37). Ruocco *et al.* also demonstrated data showing very little effect in poor immunogenic tumors with anti-CTLA-4 antibodies but reversal of tumor elicited MHC Class 1 dependent arrest with radiation and immunomodulator combination (38).

Ongoing Phase 1 and 2 clinical trials combining radiation and immunotherapy are described in *Table 3*.

Conclusions

Immunotherapy has shown a clear but modest benefit as monotherapy and combination therapy in highly immunogenic tumors. Through preliminary data, these agents have also demonstrated some scope in breast cancer and other poorly immunogenic tumors, although with some conflicting results. Identifying methods of initiating interactions between tumor cells and the immune system and augmenting the few existing interactions will determine

the success of these agents in breast cancer and other similar cancers.

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