

Immunotherapy in Breast Cancer: A Review of Literature

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Abstract

Breast cancer has ranked number one cancer among Indian females with age adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women in 2018. It is also the second leading cause of cancer death in women. Fortunately, with advances in detection and treatment, death rates from breast cancer are declining. More recent advancements in breast cancer therapy using novel mechanisms involving actionable cancer mutations and the body's immune system have opened up new avenues for reducing the death rate further. Breast cancer is one cancer that, although not originally thought to be immunogenic, has had many encouraging results in the past few years. We aim to provide a succinct overview of breast cancer immunotherapy as well as possible future directions.

Keywords: Cancer • Breast cancer • Immunotherapy • RNA

Introduction

The basis for immunotherapy in cancer has revolved around the concept of immunogenicity. For a long time, breast cancer has been considered non-immunogenic. However, the role of the immune system in the emergence of breast cancer has been firmly established [1-3]. Random or inherited genetic and epigenetic abnormalities confer proliferative and/or survival advantages on certain cells. By targeting the new antigens created by these genetic changes, the immune system plays a central role in cancer control that can be host-protective or tumor promoting [4].

Traditional pathology and immunohistochemistry, gene expression profiling, RNA sequencing, and combined scores have been used to assess the immunogenicity of breast cancer. Traditional pathology tools allow the assessment of breast cancer immunogenicity by studying the presence of Tumor-Infiltrating Lymphocytes (TILs) and assessing their types and correlation with survival and recurrence. While TILs were not found to have a prognostic value in the overall breast cancer population or ER-positive/human epidermal growth factor receptor 2-negative (ER⁺/HER2⁻) patients, TILs were found to have a prognostic value for Disease-Free Survival (DFS) and Overall Survival (OS) in TNBC [2,5]. In patients with TNBC who had residual disease after neo-adjuvant chemotherapy, the presence of TILs was found to be associated with better OS as well as with metastasis-free survival. In ER-negative breast cancers, TILs, specifically CD8⁺ lymphocytes, were associated with better breast cancer-specific survival [5,6]. The presence of CD8⁺ lymphocytes in patients with ER-negative breast cancers was also related to longer DFS [6].

Immunogenicity of a tumor is evaluated by the assessment of its antigenicity and the latter is evaluated by assessing its mutagenicity. TNBC has the highest mutational load compared with HR-positive breast cancers and high mutational load is associated with better prognosis in TNBC and HER2⁺ compared with low mutational load in the same type of breast cancer [7,8].

Review of Literature

Several strategies have been used to harness the power of the immune

system and redirect it to eradicate breast cancer or to induce immune dormancy like Breast cancer vaccines, Monoclonal Antibodies (MAbs), Antibody-Drug Conjugates (ADCs), Checkpoint inhibitors, Stimulatory molecule agonist antibodies, Combination immunotherapy trials.

Monoclonal antibodies are an integral part of our armamentarium in the fight against cancer. They can be divided into those that target the immune system (checkpoint inhibitors) and those that target oncogenic membrane receptors (HER2) or other surface molecules of unknown function (CD20). Trastuzumab is a standard component of the treatment of HER2-positive breast cancer. Its development in the 1990s was considered a landmark achievement in the field of targeted therapy [9]. The failure of TKIs to make a significant difference in the outcomes of patients suggests that blocking the oncogenic stimulation of HER2 might not be the main mechanism of action of HER2-targeting MAbs. The Finer investigators found that every 10% increase in TILs was associated with decreased distant recurrence and other studies found that TILs had a prognostic and predictive value as their presence predicted for higher pCR to Trastuzumab-containing chemotherapy and better DFS [4,10]. A meta-analysis of neo adjuvant RCTs showed that the pCR rate was significantly higher in patients with lymphocyte-predominant breast cancer in HER2-positive breast cancer settings, with an absolute difference of 33.3% (95% CI=23.6%-42.7%) [11].

TDM1 or ado-Trastuzumab emtansine is now FDA approved for patients with HER2-positive MBC whose disease has progressed on trastuzumab and a taxane based on the results of the EMILIA (Emtansine versus Capecitabine plus Lapatinib in patients with previously treated HER2-positive advanced breast cancer) trial [12]. Despite the success of TDM1 in HER2-positive breast cancer, 50% of the patients did not respond on the EMILIA trial. To meet the need of those patients, other ADCs targeting HER2 are being investigated. Three ADCs targeting HER2 are using Trastuzumab, DS-8201a (drug/target: Exatecan/Topoisomerase I), SYD985 (drug/target: Duocarmycin/DNA), and ADCT-502 (drug/target: Pyrrolobenzodiazepine dimer/DNA). The other ADCs targeting HER2 are using different MAbs and different drugs and targets. 102 Three ADCs are being developed for TNBC [13].

Targeting programmed death-1 and programmed death-ligand 1 (PD-1/PD-L1) in breast cancer appears increasingly appealing after the success of such an approach in other cancers. The PD-1 receptor inhibits innate and adaptive immunity when upregulated on immune cells and engaged by its ligand, PD-L1 [14]. Currently, results from a phase Ib study in heavily pretreated patients with TNBC who received Pembrolizumab demonstrated an acceptable toxicity and good safety profile [15]. The Keynote-086 trial is a phase II study with Pembrolizumab in patients with metastatic TNBC as first-line (cohort B; n=52; 100% were positive for PD-L1 expression) and subsequent line therapies (cohort A; n=170; 60% were positive for PD-L1 expression) [15]. Overall response rate (ORR) was 4.7% in cohort A and 23% in cohort B. The 1- and 2-year OS rates were 37% and 18% in cohort A and

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Table 1. Three ADCs are being developed for TNBC.

Name	ADC target	Drug class/target	Latest development stage	Sponsor
Sacituzumab govitecan IMMU-132	Trophoblast cell surface antigen 2 (TROP2)	Irinotecan/topoisomerase I	Metastatic TNBC Phase II	Immunomedics NCT02574455
Glembatumumab vedotin CDX-011 CR011-vc MMAE	Glycoprotein nonmetastatic b (GPNMB)	Auristatin/tubulin	Metastatic TNBC Phase II	Celldex Therapeutics NCT01997333
SAR566658 anti-CA6-DM4	CA6 sialoglycotope of	Maytansinoid/tubulin	Metastatic TNBC Phase II	Sanofi NCT02984683

Table 2. Ongoing phase 3 chemo-PD I/PD-L1 inhibitor combination trials in advanced breast cancer.

Clinical trials. Govidentifier	Trial name	PD1/PD-L1 inhibitor	Chemotherapy partner	Study design	Study population	Primary endpoint
NCT02425891	IMpassion-130	Atezoliz umab	Nab-paclitaxel	Randomised, double-blind, placebo-controlled	Study population Treatment naïve mTNBC	PFS; OS
NCT03125902	IMpassion-131	Atezoliz umab	Paclitaxel	Randomised, double blind, placebo-controlled	Treatment naïve mTNBC	PFS
NCT03371017	IMpassion-132	Atezoliz umab	Investigator's choice: Gemcitabine/ Carboplatin; Capecitabine	Randomised, double blind, placebo-controlled	TNBC progressing within 12 months from last treatment with curative intent	OS
NCT02819518	Keynote-355	Pembro lizumab	Nab-paclitaxel; Paclitaxel; Gemcitabine/ Carboplatin	Part1: Open-label, unblended safety run-in Part2: Double-blind, placebo-controlled, randomised	Treatment naïve mTNBC	PFS; OS; safety

63% and 47% in cohort B, respectively. Similar results for ORR were obtained using single-agent Atezolizumab in frontline (first line 23%) and subsequent line settings (second line 4% and third line 8%) (Table 1).

CTLA-4 is another immune checkpoint that is being targeted in breast cancer. Similar to the PD-1/PD-L1 inhibitors, most ongoing clinical trials involving CTLA-4 generally revolve around melanoma. Ipilimumab is a CTLA-4 MAb FDA approved for the treatment of unresectable melanoma. It is currently being used in a phase I study examining its safety in combination with a new anti-B7-H3 mAb, Enoblituzumab, to patients with multiple refractory cancers, including TNBC. Ipilimumab is also being combined with Entinostat and Nivolumab in a phase I study for metastatic HER2-negative breast cancer as well as with just Nivolumab in a phase II studies for patients with recurrent stage IV HER2-negative breast cancer. There are other ongoing trials evaluating the combination of a CTLA-4 inhibitor, with additional treatments [11]. There is a phase II study of Tremelimumab (CTLA-4 inhibitor) with a PD-L1 inhibitor, MEDI4736, in patients with HER2-negative breast cancer to look for the safety and efficacy of this regimen. A phase I study has already been completed with the combination of Tremelimumab and Exemestane in patients with hormone-responsive advanced breast cancer.

The PD-1 MAbs (Nivolumab and Pembrolizumab) and PD-L1 MAbs (Atezolizumab, Durvalumab, and Avelumab) are being tested in many combination clinical trials. Some trials are exploring combinations with chemotherapy and others with biological agents targeting HER2-positive or hormone receptor-positive breast cancers. However, most of these studies are designed for TNBC due to its known immunogenicity and results from single-agent checkpoint inhibitors that showed efficacy in this subtype [8].

Traditionally, the effect of chemotherapy has been explained by the induction of apoptosis of cancer cells after interrupting their cell cycle apparatus. However, alternative mechanisms involving the immune system have been recently invoked. Taxanes, doxorubicin, and Cyclophosphamide, which are standard chemotherapeutic agents in the treatment of breast cancer, are known to have major effects on the immune system in animals and human experiments. For example, Taxanes, as a class, increase serum IFN- γ , IL-2, IL-6, and GM-CSF levels as well as reducing the levels of IL-1 and TNF- α . Paclitaxel given neoadjuvant increases the levels of TILs within the tumor itself (Table 2).

The immune effects of chemotherapy may be summarized by rendering dying cancer cells more visible to the immune system by exposing their

TAA, stimulating the innate immune system, stimulating T-cell differentiation, promoting a cytokine profile that increases the likelihood of TH1 polarization, inhibition of MDSCs and M2 macrophages, and suppression of FOXP3⁺ Treg cells. Acknowledging these mechanisms is of major importance to optimize their benefit and minimize toxicity to the immune system that becomes an important executioner of chemotherapy effect [2,9].

The overall goal of cancer immunotherapy is the activation of the immune system against the cancer. Vaccination has traditionally been to boost the latent immune response to tumour-specific antigens. Approaches have included cell-based protocols involving immunization with whole autologous or allogeneic tumours, as well as antigen-based strategies involving immunization with proteins or peptides overexpressed in tumours and under expressed in normal tissues. HER2 and MUC1 are the predominant antigens used in human breast cancer vaccine trials. Although vaccination using these antigens may demonstrate tumour-reducing effects, neither antigen provides any tissue or tumour specificity because both are expressed in a variety of normal tissues and tumours raising concerns about the possibility of off target damage if a robust immune response is developed.

Discussion

However, despite the lack of inherent tissue specificity of HER2 and MUC1, these concerns about systemic autoimmune sequelae have not been substantiated so far. Tumour-associated carbohydrate antigens are pan-immunogens that elicit responses to several antigens, thus achieving the same goal as a multivalent vaccine. To overcome their low immunogenicity, investigators have used CMPs that seem to elicit a broad-spectrum antitumor reactivity. Here again, the activation of immune responses against TACAs raises concerns regarding the balance between "tumour destruction" and "tissue damage," as TACAs are also expressed on normal tissues. The evidence gleaned from phase I and II trials is reassuring. It is not clear which subtype of breast cancer would benefit from this approach.

Monoclonal antibodies are an integral part of our armamentarium in the fight against cancer. They can be divided into those that target the immune system and those that target oncogenic membrane receptors (HER2) or other surface molecules of unknown function (CD20). Anti-HER2 antibodies have changed the outlook of this disease. The failure of small molecules that inhibit the oncogenic stimulation of HER2 and the lack or minimal response to these

antibodies in tumours that lack TILs suggest that their action is more immune mediated than oncogenic mediated.

Monoclonal antibodies that inhibit checkpoints (checkpoint inhibitors) are changing the paradigm of care in many solid tumours. The first results of their use in breast cancer suggest that they are the most effective in TNBC. Their use is being investigated in the other subtypes. Due to the low immunogenicity of luminal A and B breast cancers, a combination strategy using vaccines to stimulate the immune response followed by checkpoint inhibitors is rational but its clinical usefulness remains to be proven.

Conclusion

Finally, the immune mechanism of chemotherapy is being increasingly recognized. Its contribution in the total effect of chemotherapy relative to the direct cytotoxic effect is not known. Any further development of chemotherapy in the future should take this aspect into consideration to maximize the immune stimulatory effect and minimize the immune suppressive effect of chemotherapy.

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