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Review Article

Immuno-oncological era of breast cancer: A progressive path to better treatment

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ABSTRACT

Breast cancer was initially thought to be less immunogenic; however, extensive studies in recent years have transcended into one having high mutagenic potential. The molecular classification of breast cancer has taken giant strides, as to having subtypes in triple negative breast cancer (TNBC) as proposed by Lehmann and group. This recent development has been studied extensively in the immunotherapy trials, the most recent one being the IMPASSION 130 trial which introduced the drug – Atezolizumab. In addition, tissue infiltrating lymphocytes have also been researched in the treatment of residual tumors in post-neoadjuvant scenarios. Vaccines, CART cell therapy, and antibodies are being developed in breast cancer just like the immunotherapeutic strategies in other cancers. This review is an attempt to present the ongoing developments in the field of immunotherapy in breast cancer with highlights in TNBC's, metastatic breast cancer, and hereditary BRCA positive cancers in particular.

Keywords: Immunotherapy, Tissue infiltrating lymphocytes, Tumor microenvironment, Breast cancer, immune evasion

INTRODUCTION

Malignant disease in breast cancer is seeing advances to a great extent, due to development in molecular targets. Neoadjuvant treatments leading to pathological complete response (pCR) and adjuvant treatments targeting specific molecules have helped improve survival. Tumor infiltrating lymphocytes (TIL's) as part of evaluation have gained momentum, especially in the chemosensitive solid tumors. Triple negative breast cancers (TNBC) and HER2 positive diseases particularly respond to neoadjuvant chemotherapy, where TIL's can help to predict this response. They would also be helpful in the adjuvant setting with prognostication.[1] These subtypes have high mutation rates with greater heterogeneity. Further studies would be required to prove the utility of TIL levels and TIL density in response to the treatment. There have been developments to issue international guidelines for TIL in solid tumors by the biomarker immune-oncology working group as well.[2] Breast cancer was initially thought to be less immunogenic (cold tumor) as compared to other solid tumors such as melanoma. The evolution of molecular subtypes and various other targets including TIL's has rendered them immunogenic with options of immunotherapy.[3]

Cancer cells acquire the characteristics of evading the immune system due to the genetic mutations in the native tissue. The existence of anticancer immunity is proven by the success of immune checkpoint inhibitors in various malignancies.[4] The advances in the field of vaccination for

Table 1: Various studies regarding immunochemotherapy, targeted therapy, and immunotherapy and dual immunochemotherapy.

Immunochemotherapy	Phase of study	Tumor type	Combination chemotherapy agent
Chemotherapy+ immunotherapy			
Atezolizumab	Phase 3	TNBC	Paclitaxel
Pembrolizumab	Phase 3	TNBC	Nab paclitaxel
Targeted therapy+immunotherapy			
Atezolizumab	Phase 1	HER2+	Paclitaxel
Pembrolizumab	Phase 3	HER2+	HER2 activated T cells
Dual Immune chemotherapy			
Ipi/Nivo	Phase 1	MBC	Entinostat

solid tumors with a better understanding of immunological pathways would mark the renaissance in breast cancer immunotherapy as well.[5] The concept of immunoediting including elimination, equilibrium, and escape could help us define the various targets of immunotherapy.[6-8] Mortality in breast cancer amounts to about 20% despite the various modalities of the treatment. Biomarker assessment could help in this regard, enhancing the utility of markers like PDL-1 approved by the FDA.[9] Various combinations of immune checkpoint inhibitors can be a therapeutic strategy based on the evaluation of these markers.[10] Metastatic breast cancer (MBC) is another group that is highly heterogenic with poor response to therapy. Attempts to increase survival include changing patient characteristics, tumor characteristics, physician expertise and clinical situations including surgery, availability of chemotherapy, and radiation.[11] The introduction of immunotherapy in early breast cancers comes with the idea that the tumor becomes less immune responsive and immune resistant over time.[12] Immuno-oncology has also penetrated into the field of treating metastatic breast secondary's.[13] A good biomarker should be reproducible, affordable, and accessible to pathologists to be used consistently.[14] The evolution of immunotherapy beginning with radiotherapy and moving on to chemotherapy followed by targeted treatment has now progressed to involve immune check point inhibitors.[15,16] The contribution to this field of immunotherapy has been recognized by the award of Nobel prize to Allison and Tasuku Honjo for the discovery of Cytotoxic T lymphocyte associated protein 4 and PDL1. With the advent of anti PDL1 trials, understanding the immunology of these tumors becomes more relevant.[7] The tumor microenvironment, various host tumor interactions, targeting elements in breast cancer necessitates the review of the literature in immune oncology.[8,9]

TIL'S: IN POST-NACT SETTING

NACT is a standard of care in most of the operable breast cancers due to the advantage of down staging and making breast conservation surgeries possible. The added advantage of achieving pCR signifies better outcome. The HER2+ breast cancers and TNBC's respond better to NACT, by attaining pCR. While some patients without pCR survive longer, some patients with pCR have early recurrences. This makes pCR an unreliable surrogate marker of response. The need for newer biomarkers led to the use of combination of residual cancer burden and TIL for assessment of response and predicts response. TILs are usually assessed with hematoxylin and eosin stain making it feasible in routine practice. They are classified into two categories: Hot (TIL rich and inflamed) and cold (TIL poor and non-inflamed). The present evidence of chemotherapy in TNBC post-NACT is observation. Alternative option is use of Capecitapine, which showed reduced mortality. TIL assessment in these cases with residual disease post-NACT could predict disease recurrence and overall survival. RING study was conducted by the working group to standardize TIL evaluation. TILs are particularly assessed after NACT to evaluate residual disease as they are expected to elicit antitumor response. TIL was initially evaluated in the samples of Geparsixto group. A 20% increase in pCR rate was seen with 10% increase in TILs. Areas post-NACT are categorized into areas of regression and residual cancer burden. The other areas of normal lobules, fibrosis, *in situ* carcinoma, and necrosis have to be excluded from the study. Stromal TILs account for about 6.5% including CD4 cells, CD 20+ cells, and T regulatory cells. The presence of TILs in *in situ* carcinoma signify aggressive disease with higher nuclear graded, higher necrosis, ki67 and triple negative, and HER2+ subtypes.[1,17-19]

History of cancer immunity dates back to Burnet who described the immune surveillance theory 50 years ago. T-cells form an important part of adaptive immunity with developments in the field of cancer immunotherapy. Immunoediting proposed by Schreiber included three phases. Elimination phase incudes elimination of tumor cells by natural killer cells. Tumor cells undergo genetic and epigenetic changes which exhibit malignant behavior while being dormant due to antitumor activity. In the escape phase, tumor cells escape the immunogenicity and proliferate into tumor masses. These changes are driven by neo antigens associated with passenger and driver mutations. TNBC's and HER2 positive subtypes have higher tumor mutation burden as compare to the luminal subtypes. A 10% increase in TIL is known to cause lesser TNBC tumor recurrence and offers better survival according to the BIG 2-98 and ECOG group trials. This immunomodulation forms the basis of immunotherapy. Certain combination chemotherapy adds to reduction immune response, hence, combined with

immune check point inhibitors.[2,20,21] [Table 1] KEYNOTE 012 and JAVELIN trials assessed response to immunotherapy including pembrolizumab and Avelumab.[22,23]

COMBINATION IMMUNOCHEMOTHERAPY

Circulating tumor cells and circulating tumor DNAs are soluble proteins which serve as useful biomarkers to predict response to therapy. The issue with development of these techniques has been its' reproducibility. Prediction of benefit of chemotherapy and targeted therapy has been assessed with the help of certain genomic assays such as Oncotype Dx, Mammaprint, and Prosigna which have been validated with multiple trials.[9-11]

Early breast cancers have two different approaches to immunotherapy based clinical trials – 1. Immunogenicity driven approach based on immune characteristics. 2. Subtype driven approach based on certain novel tests and clinical criteria. Immunotherapy has an advantage of chemo de-escalation reducing the toxic side effects of chemotherapy and minimizing resistance to chemotherapy.[12] Next generation sequencing has made giant advances in the field of breast cancer. It identifies various mutations associated with breast cancer, adding prophylactic surgeries, hormonal therapy, and PARP inhibitors to the armamentarium the armamentarium of breast cancer therapy.[13,14]

FUTURE OF IMMUNOTHERAPY

Tumor cells benefit from aerobic glycolysis in the presence of hypoxia. Hypoxia on the other hand is detrimental to immune cells. Metformin can cause hypoxia in the tumors, hence, being investigated in this direction.

Vaccines against cancer have been successful in cervical cancers but have not seen light in breast cancers and other solid tumors. Cancer vaccines have least toxicity as compared to all other forms of therapy. Peptide vaccines anti-HER 2 vaccines are a few attempts in this regard. HER 2 directed peptide vaccines have been successful and shown better 5-year disease-free survival in the present study. Another strategy is to employ transfer of adoptive immunity to chimeric antigen receptor T (CART) cells.[4,15,23]

CONCLUSION

MAP kinase pathway and its' targets form the most recent approaches in immunotherapy. Stimulator Interferon Genes agonists are a therapeutic strategy serving as direct agonists of innate immunity and overcome tumor characteristics. Alterations in the tumor microenvironment bring about significant changes in the response to therapy, providing the rationale for immune check point inhibitors. TILs both stromal and intratumoral have given insights into tumor immunogenicity, exploring possibilities of therapy post-chemotherapy. All the advances in the field of immunotherapy have targeted specific subtypes such as TNBC and metastatic disease. With the advent of tumor vaccines and CART cell therapy, the field of immunotherapy is ever expanding. Personalized patient profiling and targeted therapy are the way forward in cancer medicine.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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