Review Article

Immunotherapy in Breast Cancer

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Abstract

Over the last few years, the developments around cancer immunotherapy have led to a paradigm shift in the treatment of many different cancers and leukemias, in particular, melanoma, renal, bladder, and lung cancers with a remarkable impact on response rate and most importantly, overall survival was noticed. Breast cancer is most commonly considered to be a "noninflamed" cancer, and hence, this shift has been less marked within its treatment. However, some subsets of breast cancer, most notably triple-negative breast cancer, are deemed to be more "inflamed" and therefore may prove to be an appropriate cohort for immunotherapy.

Keywords: *Breast cancer, history, immunotherapy, Iran*

Introduction

Over the past half-century, advancements in our understanding of breast cancer biology have transformed the current landscape of disease management, leading to improvements in early detection strategies, development of breast-conserving surgery techniques, utilization of cytotoxic chemotherapy regimens for the treatment of both local and metastatic disease, engineering of targeted therapies against the hormone pathway and human epidermal growth factor receptor 2 (HER2/neu), and employment of hormonally directed therapies as a preventive measure.[1] This evolution in breast cancer management has led to a one-third reduction in mortality since the year 1990,[2,3] yet breast cancer remains the most prevalent malignancy in women and the second-most common cause of cancer-related death worldwide.[4,5] The recognition of the role of the immune microenvironment can be manipulated to generate effective therapeutic strategies. We present here a review of the major approaches to immunotherapy in breast cancers, both successes and failures, as well as new therapies on the horizon.

Immune Microenvironment in Breast Cancer

Breast tumors are complex systems comprising two primary components: the cancer cells typically derived from malignant transformation of mammary ductal or lobular cells, and the surrounding stromal compartment composed of a variety of normal host cells (e.g., fibroblasts, immune cells, and cells of the vasculature) and extracellular matrix molecules that are conscripted to provide a biochemical and structural milieu supportive of tumor development, progression, and metastasis.[6-10] One major class of stromal host cells, the immune infiltrate, has garnered considerable attention for its exploitability in the treatment of many malignancies, including breast cancer.[11]

The presence of tumor-infiltrating lymphocytes (TILs) has long been linked to a favorable prognosis. However, only our current understanding of breast cancer subtypes has led to the realization that the prevalence of TILs, as well as their prognostic and predictive meaning, vary between these subtypes. The highest prevalence of TILs can be observed in triple-negative breast cancers (TNBC) and HER2-positive disease, whereas TILs are less abundant in luminal type breast cancers, with the lowest amount of immune infiltration being observed in luminal A-like disease.[12]

In the adjuvant setting, each 10% increase in TILs has been associated with a 19% relative risk reduction for distant recurrence in TNBC. About 10% of TNBC can be categorized as lymphocyte-predominant breast cancer, whereas 15%–20% show no

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relevant lymphocyte infiltrate. In TNBC patients who do not achieve a pathological complete response, the presence of abundant TILs in the residual tumor, which can be observed in about 10% of cases, predicts a good prognosis even in the case of residual nodal involvement.[13]

In HER2-positive breast cancer, TILs and immune gene signatures provide similar prognostic and predictive information; however, the data are more complex, possibly because of the use of HER2-directed antibodies such as trastuzumab and pertuzumab which at least in part rely on immunologic effects such as antibody-dependent cellular cytotoxicity to achieve response and might attract new TILs in tumors which were negative before therapy.[14-18] In the estrogen receptor (ER)-positive breast cancer, the prevalence of TILs is significantly lower, and their impact seems less pronounced at least in low-grade luminal A-like disease.[19]

Immune Checkpoint Inhibition in Breast Cancer

The activation of T-cells requires two distinct signals. The first signal is delivered by the interaction of an antigen-specific T-cell receptor and the antigen complex. Tumor-associated antigens or neoantigens are released from dying cancer cells. After their uptake by antigen-presenting cells (APCs) such as dendritic cells, they are processed into small peptides which are presented on MHC Class I and II molecules to CD8+ and CD4+ T-cells to elicit an antitumor immune response. The binding of B7 molecules on the APCs to CD28 on T-cells delivers the second positive signal for antigen-specific T-cell activation. Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), which is physiologically unregulated on T-cell activation, provides feedback by delivering an inhibitory signal to the T-cell on binding to B7 molecules. This serves as an important mechanism to control physiologic T-cell activity. At the APC/T-cell interface, an array of co-stimulatory and inhibitory molecules has been identified, which are important for controlling T-cell responses. This negative immune checkpoint has been successfully exploited as a therapeutic target for anti-CTLA-4 antibodies. Ipilimumab, an antagonist antibody against CTLA-4, was the first immune checkpoint inhibitor to be approved for the treatment of metastatic melanoma.

Programmed cell death protein 1 (PD-1) [Figure 1] plays an important role in subsiding immune responses and promoting self-tolerance through suppressing the activity of T-cells and promoting differentiation of regulatory T-cells.[20]

The PD-1/PD-L1/2 pathway constitutes a second major counterregulatory pathway. The PD-1 receptor on T-cells binds to its cognate ligands, PD-L1 and PD-L2, which are expressed on the tumor as well as immune cells within the tumor microenvironment. The binding leads to a shutdown of T-cells within the tumor during the effector phase. However, the PD-1: PD-L1/L2 [Figure 2] pathway also mediates potent inhibitory signals to hinder the proliferation and function of T effector cells and have inimical effects on antiviral and antitumor immunity. Therapeutic targeting of this pathway has resulted in the successful enhancement of T-cell immunity against viral pathogens and tumors.[21]

Monoclonal antibodies directed against PD-1 as well as PD-L1, for example, pembrolizumab and nivolumab, have been approved for the treatment of a variety of metastatic solid tumors such as melanoma and nonsmall-cell lung cancer (NSCLC), and clinical trials continue to provide evidence of efficacy in a growing number of tumor entities and hematologic malignancies. The remarkable results observed in melanoma and NSCLC have set the ground for a race in clinical development in most tumor entities.

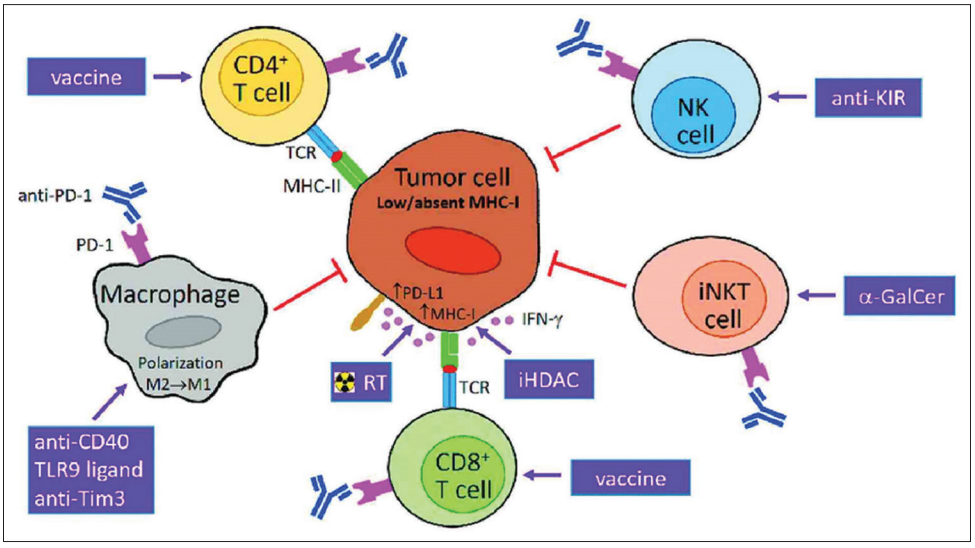

Figure 1: Potential usage of programmed cell death protein 1 blockade in combination therapy of tumors with downregulated major histocompatibility Class I expression

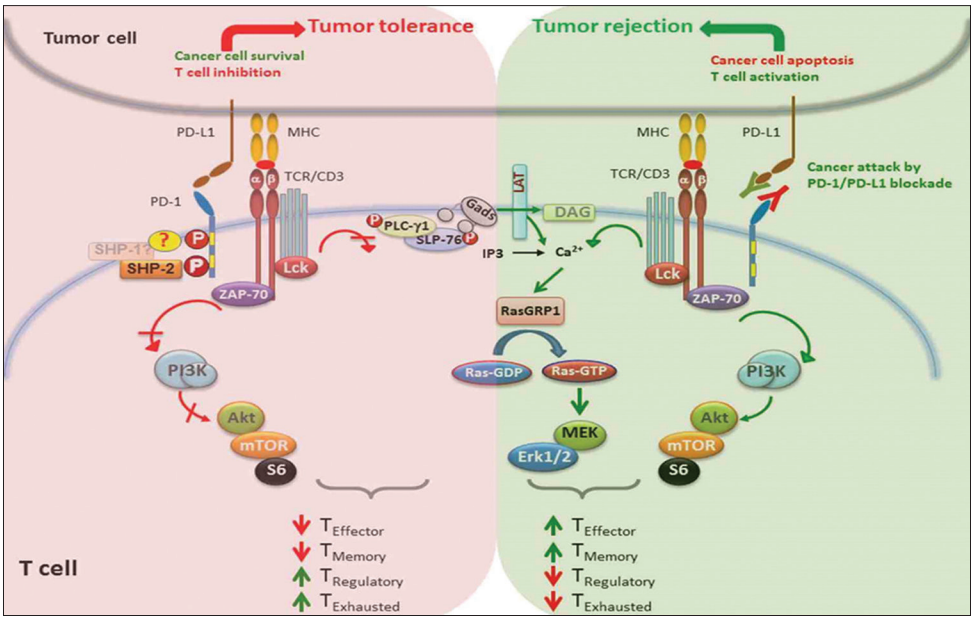

Figure 2: PD-1/PD-L1 blockade enhances tumor rejection by activating T-cells. (Left) when PD-1/PD-L1 pathway is active. Promotes survival of cancer cells through anti-apoptotic signals mediated through PD-L1 and inhibits signaling pathways that lead to activation and expansion of T-cells that recognize tumor antigens. (Right) Blocking the PD-1/PD-L1 immune checkpoint pathway by anti-PD-1 or anti-PD-L1 antibodies suppresses cancer cell survival and enhances the antitumor responses of T-cells, leading to tumor regression and rejection. PD-1: Programmed cell death protein 1

A lot of effort has been put into evaluating PD1 and PD-L1 as predictive biomarkers for the benefit from PD-1/PD-L1 targeted therapies. The focus has been on PD-L1 expression, as PD1 expression can be found on a variety of different cell types, including CD4+, CD8+ T-cells, B-cells, Tregs, and natural killer cells, and its predictive value is considered limited. However, there are several methodological concerns with regard to the determination of PD-L1 expression. First, so far, there are no standardized detection methods, and correlative biomarker studies in different clinical trials have used different antibodies for detection by immunohistochemistry (IHC) as well as variable cutoffs for positivity. In breast cancer, using the same cutoff for PD-L1 positivity, positivity rates within the same breast cancer subtype differ by as much as 30% (19.4% vs. 55.4%).[22] This is paralleled by the observation that there is only limited concordance between IHC- and mRNA-based determination of PD-L1 expression. Furthermore, although in several cancer types significant association between PD-L1 expression and benefit from immune checkpoint inhibitors has been observed, in all of these studies some degree of benefit in tumors deemed PD-L1-negative has consistently been seen, currently limiting the use of IHC-based PD-L1 to select patients for immune checkpoint inhibitor therapies. The strongest PD-L1 expression can be found on infiltrating immune cells as opposed to cancer cells, and this seems to play the most important predictive role. Therefore, to regard PD-L1 expression on tumor cells as the main mechanism of immune escape is far too simplistic.[23]

Anti-Programmed Cell Death Protein 1 Antibodies

The safety and efficacy of single-agent pembrolizumab, a monoclonal anti-PD-1 antibody, has been investigated within the phase Ib KEYNOTE-012 trial in patients with metastatic TNBC. The rationale for early trials of PD-1/PD-L1 blockade in breast cancer to focus on TNBC is based on the putative higher genetic instability with presumed higher mutational load and neoantigens. In addition, TNBCs contain larger numbers of TILs, and there is a huge unmet need in this subtype. Patients enrolled in the trial were selected for PD-L1 positivity by a threshold of 1% using the 22C3 antibody. About 59% of the 111 screened patients were positive. Pembolizumab was administered at 10 mg/kg every 2 weeks. In the 27 patients evaluable for efficacy, an objective response rate of 18.5% could be observed at the first report, including 1 complete response. An additional 26% of patients were reported to have had the stable disease as their best response. The median duration of response had not been reached at the time of the presentation of the results, reflecting the durability of responses observed within the trial. Treatment-related adverse events (AEs) were mostly mild and manageable and included 5 Grade 3/4 events. However, 1 treatment-related death due to disseminated intravascular coagulation was also reported, as were the typical immune-related AEs.[24] Based on these results, the Phase II KEYNOTE-086 is currently recruiting patients with metastatic TNBC, and a large Phase III trial (KEYNOTE-119) is in preparation. In addition, the Phase Ib KEYNOTE-028 trial investigated the efficacy of pembrolizumab in patients with ER+/HER2−,

PD-L1-positive metastatic breast cancer. Using the same antibody and cutoff for PD-L1 positivity, only 19% (n = 48) of the screened population (n = 248) tested PD-L1-positive, reflecting the differences in PD-L1 expression within the tumor and its environment between luminal disease and TNBC. The reported response rate within the 25 patients enrolled and evaluable was 12%. All of the three responders remained on the study treatment for >26 weeks, with the median time of response not yet reached at the time of presentation of the study at the 2015 San Antonio Breast Cancer Symposium.[23]

Anti-PD-L1 Antibodies

The monoclonal anti-PD-L1 antibody atezolizumab (MPDL3280A) has been evaluated for efficacy and safety in patients with PD-L1-positive metastatic TNBC. The trial at the time of reporting had enrolled 27 patients in the TNBC cohort, selected for PD-L1 positivity defined as IHC staining on at least 5% of immune cells using the SP142 antibody. Subsequently, patients unselected for PD-L1 expression were enrolled, but results for this cohort have not been presented. About 69% of screened TNBC patients tested positive for PD-L1. Atezolizumab was administered at doses of 15 or 20 mg/kg or a fixed dose of 1200 mg every 3 weeks. The 27 patients enrolled were heavily pretreated, with 85% of them have received more than 4 lines of prior systemic therapy. The trial reported a 24% response rate for the 21 evaluable patients, including three partial and two complete responses. The median duration of response had not been reached.[24] An additional Phase I trial, which was recently reported in abstract form at the 2015 San Antonio Breast Cancer Symposium, investigated the combination of atezolizumab and nab-paclitaxel in metastatic TNBC unselected for PD-L1 expression. The trial included 32 patients, 24 of which were assessable for efficacy. The confirmed overall response rate (ORR) within the trial was 41.7% and the investigator-assessed unconfirmed ORR 70.8%. Considering that 87% of patients had received prior taxanes and that the response rate in patients treated in the third or further line was still 28.6%, these early results are encouraging. A randomized Phase III trial of nab-paclitaxel in combination with either atezolizumab or placebo as first-line therapy for patients with TNBC is currently ongoing (IMpassion130, NCT02425891). The monoclonal anti-PD-L1 antibody avelumab has been evaluated for efficacy in patients with metastatic breast cancer unselected for subtype or PD-L1 expression within the expansion phase of the solid tumor Phase Ib JAVELIN trial. The trial recruited 168 patients, including 34.5% of patients with TNBC, 42.9% ER+/HER2-patients, and 15.5% HER2+ patients, as well as 7.1% with unknown subtype. Patients received single-agent avelumab (10 mg/kg every 2 weeks) until disease progression. The ORR for the entire study cohort was only 4.8%. Within the specific subtypes, the ORR was 8.6% for TNBC patients, and 2.8% and 3.8% for ER+/HER2− and HER2+ patients, respectively. Exploratory analyses suggested higher efficacy in patients with PD-L1-positive infiltrating immune cells (cutoff >10%). However, this subgroup included only 12 out of 124 patients evaluable for PD-L1 expression. To date, more than 50 clinical trials are ongoing or about to start investigating immune checkpoint inhibitors in breast cancer including combinatorial immune checkpoint blockade strategies, as well as novel agents (e.g., durvalumab), targets, and trials in the neoadjuvant setting.[25]

Conclusion

Immune checkpoint inhibitors targeting PD-1 and PD-L1 have demonstrated clinical activity in metastatic breast cancer, with response rates ranging from 5% to 24%, varying by subtype and PD-L1 positivity. The durability of response reported in other tumor entities has also been observed in breast cancer. PD-L1 positivity might enhance the chance of benefiting; however, patients with PD-L1-negative tumors may also respond. Despite the encouraging signals from these early trials, most patients treated with single-agent antibodies targeting the PD-1 pathway do not respond. Thus, additional predictive biomarkers are crucial to select patients for the best treatment strategies. In addition, intelligent combinatorial strategies have great potential to enhance efficacy. Such strategies include the addition of standard therapies (e.g., chemotherapy, radiotherapy) to PD-1/PD-L1 blockade in patients with larger tumor burden as well as the combination of different checkpoint inhibitors such as CTLA-4 and PD-L1 antibodies, which has recently been tested for metastatic melanoma with remarkable efficacy compared to single-agent CTLA-4 blockade alone.[26-28] Further attempts to enhance the efficacy of immune checkpoint inhibition follow the strategy of increasing the number of TILs, like breast cancer vaccines and adoptive T-cell therapies, and of depleting or blocking immunosuppressive cells from the tumor microenvironment, and are currently under investigation.[29,30]

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Conflicts of interest

There are no conflicts of interest.

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