Breast Cancer Immunotherapy: Is It Ready for Prime Time?

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Abstract

Based on the success of immunotherapeutic agents in the treatment of melanoma, and more recently in lung cancer, it is expected that immunotherapeutic strategies will be proven efficacious for the treatment of patients with many other solid tumor types. Interest in evaluating immunotherapy in breast cancer has historically been limited based on the belief that breast tumors were non-immunogenic. However, recent data have shown that breast cancers, particularly HER2-positive and triple-negative tumors, are in fact immunogenic, and that the extent of the immune response correlates with prognosis. Emerging results from clinical trials evaluating immunotherapeutic agents, including vaccines and immune checkpoint agents, in breast cancer have shown promise, leading to increased enthusiasm for immunotherapy approaches. Ongoing and future studies will evaluate novel immunotherapeutic strategies to include combination therapy regimens that will define the role of immunotherapy in the management of breast cancer.

Key words: breast cancer, immunotherapy, tumor-infiltrating lymphocytes, trastuzumab, nelipepimut-S, checkpoint blockade

Introduction

Simply stated, the goal of cancer immunotherapy is to activate a patient's immune system to recognize and kill their tumors. While this idea is not new, it is only in the past decade that immunologists have uncovered enough about T-cell regulation and the complex interplay between immune cells and the tumor microenvironment to design immunotherapeutic approaches that hold the potential to achieve this goal. With this enhanced understanding of the immune response to malignancy, over the past 5 years there have been several successes leading to FDA approval of immunotherapy agents. Sipuleucel-T, a vaccine that has been shown to prolong overall survival in patients with metastatic castration-resistant prostate cancer, was the first to be approved in 2010. Following this, 3 drugs in the class of agents known as immune checkpoint therapy have received approval, including ipilimumab (2011), a monoclonal antibody that targets the T-cell inhibitory molecule cytotoxic T-lymphocyte-associated protein 4 (CTLA-4); and 2 antibodies against the T-cell inhibitory molecule programmed cell death receptor-1 (PD-1), pembrolizumab and nivolumab (2014). While these agents were initially approved for the treatment of melanoma, in March 2015 nivolumab was approved for use in patients with metastatic squamous non-small cell lung cancer, as well. Based on these successes, it is expected that these and other immunotherapeutic agents will be approved over the next several years for the treatment of patients with many other solid tumor types, as well as hematologic malignancies.

In breast cancer, the relevance of the host immune response to the tumor has long been debated. Unlike melanoma and renal cell carcinoma, breast cancer was thought to be nonimmunogenic. However, a robust body of literature now suggests that breast cancer, particularly the more aggressive subtypes of HER2-positive and triple-negative breast cancer (TNBC), does elicit host antitumor immune responses, and that the robustness of the response correlates with prognosis.[1-4] Therefore, there is great interest in exploring the potential role of immunotherapy in treating patients with breast cancer. In this brief review, we will highlight recent reports of immunotherapeutic agents employed in breast cancer treatment, discuss select trials in progress or in development, and provide thoughts regarding strategies that could potentially lead to immunotherapy being "ready for prime time" in breast cancer.

Monoclonal Antibodies

An argument could be made that the field of breast cancer already has a successful immunotherapeutic agent. Trastuzumab, a monoclonal antibody targeting the extracellular portion of the HER2 protein, is utilized in the treatment of patients with HER2-positive breast cancer. While the benefit of trastuzumab has previously been attributed to its ability to inhibit HER2-mediated signaling, there is an increased appreciation of the agent's immune-mediated mechanisms of action.[5] Trastuzumab is a humanized IgG antibody with a conserved Fc portion, and data show a role for antibody-dependent, cell-mediated cytotoxicity mediated by natural killer cells.[6-8] In addition, small studies have demonstrated that patients administered trastuzumab generate

HER2-specific CD4+ T-cell and endogenous anti-HER2 antibody responses.[9-11]

More recently, Perez and colleagues[12] reported an immune function gene profile that was associated with improved relapse-free survival among patients with HER2-positive breast cancer treated with trastuzumab and chemotherapy in the North Central Cancer Treatment Group N9831 trial. At the 2014 San Antonio Breast Cancer Symposium (SABCS), these same investigators presented data from the N9831 trial showing that the benefit of trastuzumab was isolated to those patients whose tumors lacked tumor-infiltrating lymphocytes (TILs), and that for those with TILs already present in the tumors, there was no benefit from the addition of trastuzumab to chemotherapy.[13] The investigators suggested that these data support the concept that immune activation is an important mechanism of action for trastuzumab.

This observation contradicts recently reported data from the FinHER trial, where increases in TILs were associated with decreased distant recurrences in patients randomized to the trastuzumab arm of the study.[3] It should be noted, however, that the N9831 and FinHER trials differed with respect to the chemotherapy utilized and the duration of trastuzumab. At the 2015 meeting of the American Association for Cancer Research, data were presented from the National Surgical Adjuvant Breast and Bowel Project B-31 trial that showed that tumors with high TILs expressed upregulation of genes in immune-activation pathways involving B and T cells. More consistent with the FinHER data, a subset of patients with high expression of TIL-associated genes had greater benefit from trastuzumab than patients with low or intermediate expression.[14] Additional studies must be undertaken to determine the predictive role of TILs in HER2-positive breast cancer, as well as to validate immune-related biomarkers that could be used to identify patients likely to benefit from trastuzumab therapy.

Vaccines

At the time of this writing, there is only 1 ongoing phase III trial evaluating an immunotherapeutic agent in breast cancer. The PRESENT (Prevention of Recurrence in Early Stage Node Positive Breast Cancers with Low to Intermediate HER2 Expression with NeuVax™ Treatment) trial is evaluating nelipepimut-S, a human leukocyte antigen (HLA)-A2/A3-restricted immunogenic peptide derived from the HER2 protein.[15] This phase III registration trial follows phase I/II clinical studies evaluating nelipepimut-S combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) as a simple vaccine administered in the adjuvant setting to prevent disease recurrence in patients with high-risk breast cancer. These trials included 187 evaluable patients. The 5-year disease-free survival (DFS) rate was 89.7% in vaccinated patients versus 80.2% in controls (P = .08). Due to trial design, not all patients received the optimal vaccine dosage. For those who were optimally dosed, the 5-year DFS rate was 94.6% (P = .05 vs controls).[15] It is important to emphasize that this vaccine is being evaluated in the adjuvant setting when patients have minimal residual disease. Previous studies evaluating similar vaccines in the therapeutic setting in patients with metastatic disease showed low objective response rates (ORRs), which is likely attributable to several factors, including the immunosuppressive microenvironment of metastatic disease, as well as the fact that many of these patients were heavily pretreated.[16]

Although nelipepimut-S is derived from the HER2 protein, another important aspect of the early-phase trials is that they enrolled patients with any degree of HER2 expression in the primary tumor as determined by immunohistochemistry (IHC 1+, 2+ or 3+). Data from the early studies showed that patients with tumors that had low and intermediate HER2 expression had robust immune responses, hence the further development of nelipepimut-S in that population.[17] The PRESENT trial completed enrollment in April 2015 with 758 patients in the intent-to-treat population. It is anticipated that the primary endpoint will be reached in 2018, after approximately 36 months of follow-up.

Multiple other vaccine strategies are being investigated in patients with breast cancer, including several ongoing or recently completed phase II studies. Examples of these include additional HER2-derived peptide vaccines; an allogeneic GM-CSF–secreting vaccine; a HER2 peptide-pulsed, dendritic cell vaccine; and PANVAC, which incorporates vaccinia and fowlpox viruses genetically engineered to express the tumor-associated antigens carcinoembryonic antigen and MUC-1. All of these vaccine strategies have shown potential clinical benefit in specific disease settings in which they are being further investigated.

Checkpoint Inhibitors in Breast Cancer Treatment

Data from 2 trials of antibodies targeting the T-cell inhibitory molecule PD-1 or its ligand, programmed cell death receptor 1 ligand (PD-L1), were reported at the 2014 SABCS meeting. One was KEYNOTE-012, a phase Ib study of the anti-PD-1 antibody pembrolizumab in patients with metastatic TNBC with tumors expressing any degree of PD-L1 positivity measured by IHC performed using a proprietary anti-PD-L1 antibody.[18] The trial enrolled 32 patients, the majority of whom had more than 1 line of prior therapy. Patients were administered pembrolizumab 10 mg/kg intravenously every 2 weeks. Approximately 56% of patients experienced a treatment-related adverse event (AE), including fatigue, arthralgia, myalgia, and headache. One patient died of disseminated intravascular coagulation, which was attributed to the immune therapy. The median time on treatment was 60 days, and the ORR by RECIST 1.1 was 18.5% (5/27 evaluable patients) with 1 complete and 4 partial responses. Seven patients had stable disease. Patients with tumor response continued on treatment for over 40 weeks, with the median duration of response not reached at the time of this report. Based on these

data, a phase II trial of pembrolizumab monotherapy for patients with metastatic TNBC (KEYNOTE-086) is set to begin in 2015.

The second trial was a phase Ia study of the anti-PD-L1 antibody atezolizumab in patients with PD-L1–positive TNBC.[19] In 12 patients assessed for safety endpoints, 1 patient experienced grade 3-4 adrenal insufficiency. In 9 patients assessed for response to therapy, ORR by RECIST 1.1 was 33%. It is notable that at least 1 patient experienced pseudo-progression in axillary lymph nodes that subsequently resolved, suggesting that the response rate may have been underestimated since it was measured by RECIST 1.1 rather than the modified immune response–related criteria that have been proposed for use in immunotherapy trials.[20] A phase III trial of *nab*-paclitaxel +/- atezolizumab in patients with metastatic TNBC is planned for activation in 2015.

Future Directions

It is anticipated that the interest in identifying immunotherapeutic approaches to treat breast cancer will continue to grow, and that numerous trials evaluating immunotherapeutic approaches, including monoclonal antibodies, vaccines, and checkpoint blockade, as well as adoptive T-cell therapy with genetically engineered T cells or immunomodulatory agents such as cytokines or toll-like receptor (TLR) agonists, will become available for patients with breast cancer. The success of immunotherapy in breast cancer likely will depend on identifying the appropriate immunotherapeutic strategy for the particular disease type and stage. For example, the microenvironment of metastatic lesions is quite hostile to the immune system. Immunosuppressive cytokines and cells inhibit an effective antitumor immune response. Therefore, a simple vaccine strategy such as the nelipepimut-S peptide vaccine is unlikely to be efficacious in that setting, hence the development of nelipepimut-S in the adjuvant setting as secondary prevention. In contrast, more-toxic immunotherapeutic strategies, such as adoptive T-cell therapy, are not likely to find a role in the management of patients with early-stage breast cancer, as a significant percentage of patients will be cured with current standard-of-care therapies.

It is likely that these immunotherapies will be most beneficial when used in combination. To this point, it should be noted that although breast tumors have been shown to be immunogenic, the immune response is not always robust, with 1 study reporting the median percentage of stromal area infiltrated with TILs being only 10% in hormone receptor–positive breast cancer, 15% in HER2-positive breast cancer, and 20% in TNBC.[4] Given this lack of immune infiltrate, it is possible that such strategies as checkpoint blockade may not work. If checkpoint blockade is designed to "take the brakes off" immune cells, they would not likely be effective in the absence of an immune infiltrate. A strategy, therefore, in which 1 agent such as a vaccine or perhaps a toll-like receptor agonist is given to stimulate an immune response that can be followed and augmented by checkpoint blockade may prove more efficacious. Such a strategy is being evaluated by investigators at Johns Hopkins University,[21,22] where they are combining the GVAX vaccine with checkpoint blockade agents in pancreatic cancer, another tumor type with limited immune infiltrate.

There is significant enthusiasm for other potential combination strategies. As an example, based on evidence that trastuzumab is synergistic with anti-PD-1 therapy, there is an ongoing international phase Ib/II trial (PANACEA) in which patients with HER2-positive breast cancer that has progressed on trastuzumab will receive trastuzumab in combination with pembrolizumab. A combination strategy that our group is investigating is the use of nelipepimut-S in combination with trastuzumab. We are evaluating this strategy in 2 ongoing adjuvant vaccine trials: 1 enrolling patients with HER2 1+ or 2+ tumors, and the other enrolling patients with high-risk, HER2-positive disease.

Conclusions

Just 5 years ago, a review of breast cancer immunotherapy would have been very brief. In 2015, the subject of breast cancer immunotherapy could occupy an entire text, and we apologize to the many investigators whose work is advancing the field and which we were unable to acknowledge. Through their efforts, we are moving closer to the point where immunotherapy will be "ready for prime time" in breast cancer treatment.

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