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Current status and limitations of immunotherapy for breast cancer

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History of immunotherapy for breast cancer

When William Stewart Halsted described the radical mastectomy in1894, it was thought that a cure for breast cancer solely lay in maximally invasive and often morbid surgery. Our understanding of breast cancer has changed immeasurably in the subsequent century in which innumerable preclinical and clinical studies have demonstrated that advanced breast cancer is a systemic disease that requires a multimodality approach that includes both local (surgery, radiation) and systemic therapies (chemotherapy, endocrine therapy, and/ or immunotherapy).

The now standard multimodality approach to breast cancer treatment has greatly improved the survival of patients with breast cancer from the initial days of Halstead. The 5-year survival rate for breast cancer is >90%, making it one of the most curable cancers that we encounter in clinical practice. Notwithstanding this much improved survival rate, still over 40,000 patients die from breast cancer annually in the United States. The 90% 5-year survival rate is somewhat misleading, because breast cancers with a so-called good prognosis (i.e. hormone receptor-positive breast cancer) recur many years after treatment; the 20 year recurrence rate for estrogen receptor-positive breast cancer ranges from 10–41%. Many of these patients are diagnosed at a relatively young age, and breast cancer can become the disease that defines their survival. Even though the recurrence rate of early stage breast cancer is relatively low, this is still a sizeable number of patients given the high prevalence of breast cancer in the population. The reasons why metastatic recurrences emerge after over a decade is not completely understood, but one of the theories is that isolated tumor cells remain sequestered by the immune system for many years before some event disturbs the immunologic equipoise that has prevented tumor growth. In recent years, much attention has been devoted to exploiting the powerful cytotoxic effects of cellular immunity to target cancers. For example, stage IV melanoma, once a universally lethal diagnosis, is now a potentially a curable disease with the advent of immunotherapy.

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Immunotherapy involves enhancing immune machinery of the host (the patient) to recognize cancer as a foreign antigen and as a result lead to the destruction of the cancer cells. Anti-tumor immunity involves antigen presentation to T-cells (primarily by dendritic cells) and subsequent trafficking and infiltration of the effector T cells to the tumor bed. The infiltrating effector/cytotoxic T cells then recognize and eliminate tumor cells as they would do in the case of infection or other foreign antigens such as an allograft.

Despite the contemporary successes with checkpoint inhibitors, the field of immunotherapy has struggled to produce clinically meaningful interventions; indeed, it has been well over 100 years since William Cooley reported the phenomenon, in which the injection of a toxin led to the successful treatment against the erysipelas in the late 19th century. Since that time, countless attempts have been made to overcome cancers by harnessing this inherent anti-tumor immunity. Ever since Steve Rosenberg demonstrated that the combination of IL-2 and lymphokine-activated killer cells in the 1980s can prove effective, there has substantial interest in adaptive immunotherapy both to suppress the immune system (e.g. to promote tolerance in allotransplantation) and to enhance anti-cancer immunity in the case of cancer therapies. Multiple studies have involved the use of tumor infiltrating lymphocytes (TILs) to target cancers. The majority used the *Ex Vivo* method where patient-derived lymphocytes are cultured *In Vitro* and reinfused back into the patient after antigenic and co-stimulatory activation. Unfortunately these therapies have not yet reached prime time due to unacceptable side effect profiles or lack of efficacy.

In this review, we will discuss about the current status and limitations of immunotherapy in breast cancer and elaborate on its futures as a potentially powerful tool in the multimodality armamentarium to treat breast cancer.

Immune Checkpoint Inhibitors

The normal functioning human immune system is composed of equilibrium of opposing forces and disruption of that leads to autoimmunity or overwhelming infection and cancer. There are many intrinsic controls on immunity, one of which is immune checkpoint molecules. These metaphorical “brakes” are essential in the maintenance of normal immunologic equilibrium and their absence results in profound autoimmunity. Cancers, however, have evolved to use these molecules to evade immunologic destruction. The discovery of these checkpoints has been a milestone in cancer immunotherapy and has been recognized by the scientific community with the 2018 Nobel Prize for being awarded to James Allison at MD Anderson Cancer Center who discovered CTLA-4, and Tasuku Honjo at Kyoto University who discovered PD-1. Immune checkpoint inhibitors (ICIs) have been successful in the clinical arena in the treatment of melanoma, lung cancer, and microsatellite unstable colon cancer. Unfortunately, the success of ICIs in melanoma and lung cancer has not been realized in breast cancer. This non- responsiveness of breast cancer is explained probably by the “cold” immunologic nature of breast cancer, meaning that breast cancers are characterized typically by a paucity of infiltrating immune cells; as a result, ICIs have less of an impact. In fact, it appears that as breast cancer progresses from ductal carcinoma in situ to invasive cancer, there is a progressive decrease in the population of activated CD8+

cytotoxic T cells, suggesting that immune escape may play a substantial role in the evolution of breast cancer.

The first clinically relevant breakthrough for immunotherapy in breast cancer was reported in the IMpassion130 trial in November 2018 [1] and led to the subsequent approval of Atezolizumab and Nab-Paclitaxel for metastatic or unresectable triple negative breast cancer. This report came over seven years after immunotherapy/check point inhibitors were first approved for melanoma (ipilimumab), which highlights the current limitations of immunotherapy in treatment of breast cancer. The Impassion130 trial studied the use of Atezolizumab, aPD-L1 inhibitor, in combination with Nab-Paclitaxel in metastatic, triple negative cancer; the benefit of Atezolizumab was restricted to the population that expressed PD-L1 in >1% of the cells. The PD-L1 positive population represented 41% of the study population, and the effect was relatively small (absolute median benefit of 2.5 months survival); however, this response still represents progress in a disease with limited therapeutic options (as opposed to hormone receptor-positive or Her2 positive breast cancer).

The KEYNOTE-086 study examined the single agent pembrolizumab in metastatic, triple negative breast cancer, where an objective response rate of 21.4% and 5.7% in treatment-naïve and previously treated PD-L1 positive patients with some complete responses being seen in the treatment-naïve group[2]. There are ongoing phase III trials of pembrolizumab as monotherapy (e.g. pembrolizumab in patients with residual disease after neoadjuvant chemotherapy for triple negative breast cancer) or in combination with conventional chemotherapy. Of note, the choice of combination chemotherapy is somewhat limited, because it is important to avoid steroids when using ICIs to avoid dampening the immune response (e.g. steroids are frequently used in highly emetogenic regimens e.g. anthracyclines). To date, it appears that ICIs are most active in patients with PD-L1 high, triple negative breast cancer who have not received multiple other lines of therapy.

Patient selection for immune checkpoint inhibitor

Given the somewhat limited efficacy, substantial side effects and cost of ICIs in breast cancer, it is essential to be able to accurately select those patients who are most likely to benefit from ICI therapy. The most intuitive and basic biomarker is PD-L1 expression. PD-L1 expression was initially found to predict treatment response to ICIs in non-small cell lung cancer. In the case of breast cancer, the PANACEA trial demonstrated a marked difference in response rate between the PD-L1 positive and PD-L1 negative groups[3]. Tumor-infiltrating lymphocytes (TILs) and tumor mutational burden are other candidates as predictive markers of a tumor-immune microenvironment and consequently the response to ICI therapy. Numerous studies have demonstrated that greater numbers of TILs are associated with a greater response to the ICI therapy. Rooney and colleagues devised the concept of immune cytolytic activity (based on the measurement of gene expression of perforin 1 and granzyme B) as a correlate of effector T cell activity. Greater cytolytic activity is associated with prolonged survival highlighting the importance of the T cell response in controlling and even sometimes eliminating tumors[4]. In the case of the triple negative subtype of breast cancer contain significantly more infiltrating immune cells in comparison to hormone-positive

breast cancer, which is borne out by the lack of response to immunotherapy in hormone-positive breast cancers.

Combination with other modalities

Given the somewhat limited efficacy of ICI monotherapy in breast cancer, much interest has been focused on combining ICI and other therapeutic modalities, including conventional chemotherapy, other targeted therapies, radiation, and cancer vaccines.

Radiation therapy offers an opportunity to modulate the tumor-immune microenvironment by the upregulation of tumor-specific antigen presentation and has been demonstrated to have a synergistic effect when combined with immunologically active agents such as ICI. The beneficial effects of increased antigen presentation and resultant immune response were first described long before our contemporary understanding of the interaction of tumors and the immune system. R.H. Mole coined the term of the “abscopal effect”, which described the shrinkage of untreated tumors in patients with metastatic disease who received localized radiotherapy to only a portion of their metastatic disease. The synergistic effect of the abscopal effect of radiation and immunotherapy has been illustrated in the case of melanoma. There are several active, early phase clinical trials examining the combination of radiation and immunotherapy in breast cancer, particularly triple negative breast cancer given its richer immune microenvironment.

The combination of ICIs and targeted therapy is also attracting attention based on some encouraging preclinical and early phase clinical data. The PANACEA trial, a multicenter, single-arm phase 1b and phase 2 trial, demonstrated the efficacy of combination therapy of pembrolizumab and trastuzumab in a subgroup of trastuzumab-resistant, advanced HER2-positive cancer[3]. In this trial, PD-L1 expression was the key factor that predicted response to therapy.

CDK4/6 inhibitors and Poly-ADP ribose polymerase (PARP) inhibitors are targeted therapies that may partner well with ICIs. One CDK4/6 inhibitor is already approved for metastatic, hormone-positive breast cancer patients. Interestingly, in the preclinical studies, this drug not only demonstrated enhancement of anti-cancer immunity by modulating antigen presentation and suppressing the regulatory T cells, but it also enhanced the efficacy of ICI[5]. PARP inhibitors are approved currently by the FDA for the treatment of metastatic breast cancer in patients with a BRCA germline mutation. Similar to CDK4/6 inhibitors, PARP inhibitors increased the expression of PD-L1 and consequently enhanced the efficacy of ICI.

Cancer vaccines are also under consideration for combination therapy with ICIs. In general, the efficacy of cancer vaccines has been disappointing, but the emergence of ICIs has renewed interest in vaccines as a combination therapy with ICIs. Cancer vaccines have been studied primarily in the metastatic setting where tumors are generally less immunogenic; however, their combination with ICIs has been found to be effective in preclinical studies, and there clinical trials are ongoing to study their efficacy.

Perspective of the future direction

The current role of immunotherapy in the treatment of breast cancer is limited; however, it is not an insignificant number of patients given the frequency of breast cancer in the general population. The durable nature of the response to immunotherapy is particularly attractive, and indeed, it has led to potential cures in the setting of metastatic melanoma. If we are to see the dramatic response to immunotherapy in breast cancer that has been seen in melanoma, it is imperative that we find methods to convert immunologically “cold” to “hot” tumors, i.e. increase the TIL accumulation. As mentioned above, many attempts have been made for this purpose, including chemotherapy, radiation, targeted therapies, and cancer vaccines. There have been surgical interventions as well, such as cryoablation, radio-frequency ablation, and focused ultrasound.

The challenge of any of these approaches is that most of these approaches are immunosuppressive when the whole purpose is to make the tumor immunogenic. When the bulk tumor and the surrounding tissues are ablated, the immune cells may work more on necrotic tissue rather than cancer antigens. To this end, the future direction of immunotherapy for breast cancer should be accurate patient selection and use of ICIs in combination with immunogenic intervention with minimum immune suppression such as photoimmunotherapy.

Conflicts of Interest and Source of Funding

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